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GETUG-AFU 31: a phase I/II multi-center study evaluating the efficacy of salvage stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation therapy; study protocol.

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Abstract

Introduction. Prostate cancer is the third most important cancer in terms of mortality in men. No standard local treatment exists for patients with an intraprostatic recurrence after radiotherapy. The literature consists mainly of retrospective and small prospective series making it difficult to assess and compare these techniques. Stereotatic body radiotherapy (SBRT) could be a curative treatment for local recurrence.

Methods and analysis. We plan to perform a multicenter prospective phase I/II study including at least 47 patients. Eligible patients are patients with biochemical recurrence occurring at least 2 years after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL). The phase I primary objective is the selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity. The dose of salvage-SBRT will be selected using a Time-to-Event Continual Reassessment Method based on dose-limiting toxicity defined as grade ≥3 gastrointestinal or urinary toxicity or any other grade 4 adverse event. The phase II primary objective is to estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate (Phoenix definition). Phase II secondary objectives are: acute and late toxicities, quality of life, clinical progression free survival and overall survival. Our proposed study could provide further evidence of SBRT as a supplementary non-invasive curative treatment for local recurrence following radiotherapy.

Ethics and dissemination. The study has been funded by French National Cancer Institute (INCa-DGOS_9816) and approved by ethics committee “Ile de France III” (2017-A00008-45) for all study sites. The findings of this study will be disseminated through peer-reviewed publications and conference presentations. Trial registration number: NCT03438552

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Keywords: prostate cancer, stereotactic body radiation therapy, recurrent prostate cancer, salvage radiotherapy

ARTICLE SUMMARY

Strengths and limitations of this study funding

- Very innovative trial evaluating stereotactic body radiotherapy for recurrent prostate cancer, the only ongoing trial of this kind to our knowledge
- Clinical trial supported by the GETUG-AFU cooperative group, expert in the field, and funded by the French National Cancer Institute (INCa)
- Time-to-Event Continual Reassessment Method, a more appropriate method than the 3+3 design to quantify late toxicity in phase I radiotherapy trials
- Proof-of-concept study; therefore, further research will be required

INTRODUCTION

Prostate cancer is the third most important cancer in terms of mortality in men (after lung and colorectal cancer), and the fourth leading cancer overall.[1] In the European Union, it was predicted that 72600 patients would die from prostate cancer in 2015. The rate of recurrence/relapse of prostate cancer after primary external beam radiotherapy varies from 21% to 65% depending on the study.[2,3] Zelefsky et al. performed biopsies on 339 patients after treatment with 3-dimensional conformal radiotherapy (3D-CRT) or intensity modulated RT for T1c-T3 stage prostate cancer, with a minimum follow-up of 2.5 years.[2] They found that the rate of positive biopsy according to radiation dose was 65% for <70.2 Gy, 38% for 70.2 Gy, 27% for 75.6 Gy, and 25% for ≥81 Gy. Similarly, Zapatero studied 160 patients with stage T1c-T3b prostate cancer, treated with 3D-CRT (median follow-up was 78 months [range: 27-171 months]) with biopsies 24-36 months after RT. Thirty four patients (21%) had positive post-treatment biopsies.[3]

D'Amico reported that the 5-year prostate cancer mortality rate after biochemical recurrence in patients who received external beam radiotherapy for localized prostate cancer depended on the pretreatment PSA level and Gleason score: 24% for ≤6 score, 40% for 3+4 score, and 59% for 4+3 or higher score (p=0.01).[4] In addition, Buyyounouski reported that the interval to biochemical recurrence was an important factor in identifying men at high risk of distant metastasis and death.[5]

Prostate-specific antigen (PSA) is a validated biomarker for prostate cancer. PSA levels are extensively used to monitor response to radical prostatectomy (RP) and external-beam radiotherapy (EBRT). The recommendations of the Radiation Therapy Oncology Group (RTOG) ASTRO Phoenix Consensus Conference suggested that an increase of ≥2 ng/mL from the nadir be used to define recurrence/relapse.[6]. It is important to note that biochemical recurrence may indicate local or systemic disease recurrence, and may require prostate biopsy for confirmation particularly when local salvage treatments are being considered.[7]

A number of different salvage treatments have been used after failure of primary radiotherapy. RP is more invasive than brachytherapy, ultrasound, high-intensity focused ultrasound (HIFU), and

stereotactic body radiotherapy (SBRT). Below is a brief discussion of the results obtained with each techniques and its associated toxicity and complications.

Salvage RP is a treatment option after local recurrence following EBRT. However, the morbidity, including incontinence and erectile dysfunction, is higher than that observed with first-line RP patients. A systematic literature review [7] reported that the probability of biochemical relapse–free survival (bRFS) following salvage-RP in prostate cancer patients was 47-82% after 5 years and 28-53% after 10 years. At 10 years, cancer-specific survival ranged from 70% to 83% and overall survival from 54% to 89%. The preoperative PSA level and prostate-biopsy Gleason score were the strongest prognostic risk factors for PFS and cancer-specific survival. Salvage-RP after radiotherapy compared to primary RP has a significantly higher rate of urinary and gastrointestinal morbidity.[8] The review above [7], reported that the most frequent complications were anastomotic stricture (7-41%) and rectal injury (0-28%). The majority (50-91%) of men had erectile dysfunction before salvage-RP and 80-100% after surgery. Post-operative urinary continence ranged from 21-90%.

In a recent review, salvage brachytherapy (BT) after EBRT is reported to achieve biochemical control rates of 20% to 89% (median follow-up: 19 to 108 months).[9] Rates of genitourinary toxicities range from 12% to 87% for grade 1-2, and 3% to 47% for grade 3-4 toxicities. Similarly, the rates of gastrointestinal toxicities range from 4% to 65% for grade 1-2, and 0% to 20% for grade 3-4 toxicities. Erectile dysfunction was observed in 2% to 95% of men. A phase II study of salvage high-dose-rate (HDR) BT for treating recurrent prostate cancer after definitive external beam radiotherapy was reported by Yamada.[10] The 42 patients enrolled, with biopsy proven recurrence, were treated with salvage HDR (iridium-192) with a resulting bRFS at 5 years of 68.5% (median follow-up of 36 months [range: 2-66 months]). Acute genitourinary toxicity was observed: grade 1, 38% of patients and grade 2, 40%. Similarly, late genitourinary toxicity was observed: grade 1, 38% of patients and grade 2, 48%. In addition, 1 patient had a grade 3 urinary incontinence and 3 had grade 3 urethral strictures. Late gastrointestinal toxicities were observed: grade 1, 43% of patients and grade 2, 14%. More recently, a study of 83 prostate cancer patients with local recurrence after radiotherapy

treated with HDR BT was reported.[11] The median follow-up was 41 months. The 3-year and 5-year bRFS were 76% and 67%. A phase II study of the RTOG in 100 patients was recently presented: twelve (14%) experienced late grade 3 genitourinary/gastrointestinal adverse effects. This rate of late grade 3 toxicity (14%) was not unacceptable by the predetermined protocol specification, without any grade 4-5 events. The only factor predictive of late toxicity was implant dose, underlining the need for meticulous planning and technique to limit the final delivered dose.[12] In France, a phase II study, "Brachytherapy for Recurrent Prostate Cancer" (CAPRICUR) was recently completed.[13]

HIFU is another less invasive salvage treatments following recurrence.[14] A French group treated 290 men with biopsy-confirmed recurrent prostate cancer.[15] The mean follow-up was 48 months after HIFU. At 7 years, the cancer-specific survival rate was 80% and the metastasis-free survival rate was 79.6%. Recto-urethral fistula occurred in 0.4% of patients and 19.5% had grade 2/3 incontinence. Half of the patients also received androgen deprivation therapy (ADT). Survival without relapse at 5 years after HIFU, by D'Amico risk groups prior to their initial treatment, was 45% (favorable), 31% (intermediate risk) and 21% (high risk). In this cohort, the grade ≤3 urinary incontinence levels were 23% (favorable), 14% (intermediate risk) and 9% (high risk). Nearly 8% of patients required an artificial sphincter following HIFU. Importantly, pubic osteitis occurred in 2.5% of patients despite adherence to parameters specific to HIFU following radiotherapy.[15]

Cryotherapy is thermo-ablative treatment; the third–generation argon/helium-based cryotherapy system creates precise isotherms through ultrathin needles.[16] In a retrospective multicenter series pooling 279 patients, survival without biochemical relapse at 5 years was 54%.[17] In a paired case-controlled study, prostatectomy and cryotherapy were compared following radiotherapy. Survival without relapse (PSA nadir + 0.4 ng/mL) at 5 years was significantly lower after cryotherapy (21% vs. 61%, p<0.001); this was confirmed by the 5-year OS rate of 85%, cryotherapy, vs 95%, radical prostatectomy (p=0.001).[18] More recently, intermediate results from a study investigating third-generation cryotherapy as a salvage treatment of locally recurrent prostate cancer after radiotherapy was published.[19] The study included 32 patients, with a median follow-up of 63 months (range: 38-

92); the 5-year bRFS rate (Phoenix definition) was 43.5% and with a 5-year overall survival rate of 92.3%. Mild complications (grades 1 and 2) were reported including: mild incontinence (9.4%), acute rectal pain (31.3%), haematuria (6.3%), scrotal oedema (9.4%), urinary tract infection (3.1%), lower urinary tract symptoms (15.6%) and erectile dysfunction (57.1%). Grade 3 toxicities: incontinence (3.1%) and urethral sloughing (3.1%) were observed.

ADT alone (continuous or intermittent) is commonly given to patients with biochemical relapse after radiotherapy.[20] In a series based on data from a North American national registry (CaPSURE), 71% of patients were treated for biochemical relapse after prostatectomy or radiotherapy. ADT was initiated in 93% of these patients, and the remaining patients were treated with surgery, brachytherapy, cryotherapy, or repeat external radiotherapy.[21] ADT may cause adverse effects impacting patient's quality of life (including: hot flushes, erectile dysfunction and reduced libido, cognitive impairment, and anemia). The metabolic changes associated with hormone therapy may also increase the risk of cardiovascular morbidity. The reduction in bone mass is maximal in the first year and increases with the duration of castration; the risk of fracture is increased in patients surviving for more than 5 years.[22-23] The guidelines suggest that a simple follow-up can be implemented for local recurrence in patients with a limited life expectancy or for those who do not wish to undergo local salvage treatment. The European Association of Urology guidelines [24] recommended to perform salvage surgery in experienced centres due to the increased rate of side effects. It is recommended to offer/discuss HIFU, cryosurgical ablation and salvage brachytherapy to/with patients without evidence of metastasis and with histologically proven local recurrence and to inform patients about the experimental nature of these approaches. The level of evidence for each of these recommendations is 3.[24]

SBRT delivers highly conformal, high-dose radiation in a few fractions (hypofractionation), typically 5 to 7 fractions for prostate cancer. It is reported that tissues with a low α/β ratio, as for prostate cancer, are more sensitive to large doses of radiation per fraction. This suggests that hypofractionation may result in improved tumor control with limited toxicity. A pooled analysis of

1100 patients included in separate prospective phase II studies was performed to evaluate the effectiveness of SBRT as a first-line treatment for localized prostate cancer.[25] The SBRT was delivered by CyberKnife with a median dose of 36.25 Gy in 4-5 fractions. The 5-year bRFS rate was 93% for all patients. Thus relapse-free survival rates after SBRT compare favourably with other definitive treatments for low and intermediate-risk patients with a short follow up. SBRT is well tolerated with a low effect on quality of life.[25-28] In addition sexual function appeared to be spared in the majority of patients.[25-28]

SBRT has also been used as a salvage treatment following failure of external radiotherapy. Jereczek-Fossa et al. published data on 34 consecutive patients treated with robotic SBRT for isolated recurrent primary, lymph node, or metastatic prostate cancer.[29] Of the 34 patients, 15 patients had intraprostatic recurrence, confirmed by biopsy, and were treated with SBRT (CyberKnife) with a median dose of 30 Gy in 5 fractions. The median survival without recurrence was 13 months. Urinary toxicity was low, with a grade 3 urinary toxicity in only one patient. No case of acute or late gastrointestinal toxicity was reported. This good gastrointestinal tolerability has subsequently been confirmed.[29-32] In Fuller et al twenty-nine patients were treated in a phase II trial with SBRT for intraprostatic recurrence.[30] Eligible patients had to present biopsy-proven intraprostatic recurrence graded T1 to T3N0M0 more than 2 years post-radiotherapy and without a pre-existing grade >1 radiotherapy toxicity. The prior median dose delivered was 73.8 Gy and the median interval between the treatments was 88 months. The dose delivered to the entire gland was 34 Gy in five fractions over 5 days. With a median follow-up of 24 months, survival without recurrence was 82%. Toxicity was acceptable, with 18% grade ≥2 urinary toxicity, including one patient with a grade 4 toxicity, and no late gastrointestinal toxicity above grade 1. Particular attention should be given to patients who still exhibit urinary toxicity after initial radiotherapy.[30] Our preliminary retrospective results in 23 patients treated for this indication were published recently.[31] A total dose of 36 Gy was prescribed in 6 fractions of 6 Gy. Nineteen patients had a whole-gland and four a partial treatment. Median follow-up was 23 months (range 6 to 40 months). We observed no grade 4 or 5

toxicity. Two patients presented grade 3 toxicities. Others toxicities include urinary (5 grade 2 and 9 grade 1) and rectal toxicities (2 grade 2 and 2 grade 1).

To date, no standard local treatment exists for patients with an intraprostatic recurrence after radiotherapy.[33] A number of treatments options exist including: radical prostatectomy, brachytherapy, HIFU, cryotherapy, and stereotactic radiotherapy. The literature to date consists mainly of retrospective and small prospective series making it difficult to assess and compare these techniques. In recent years, SBRT has been used to treat localized prostate cancer in the primary setting but also as a salvage treatment after failure of radiotherapy. The initial results of these retrospective studies are promising, with respect to survival and tolerance, but further studies are required to confirm these initial results. Our proposed study will provide further evidence of SBRT as a supplementary non-invasive curative treatment for local recurrence following radiotherapy. This study could provide the foundation for prospective studies comparing the available salvage treatments after radiotherapy.

METHODS AND ANALYSIS

This study is approved by the Ethics committee “Ile de France III” (2017-A00008-45) and is registered on clinicaltrials.gov (NCT03438552). Inclusion and exclusion criteria are described in Table 1. This multicenter open-labelled phase I/II study will initially select the SBRT scheme (phase I), either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy. The effectiveness of SBRT scheme selected in phase I will then be evaluated in a single-arm multicenter phase II study.

DIAGNOSIS AND INCLUSION CRITERIA:
o Biochemical recurrence occurring at least 2 years after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL)
o T1–T2c and PSA ≤20 ng/mL and Gleason score ≤7 at initial diagnosis of prostate cancer before the initial/first treatment.
o Recurrence of prostatic adenocarcinoma proven by histology following radiotherapy by transrectal or transperineal sextant biopsies of the two lobes of the prostate, with a minimum of 12 biopsies, irrespective of Gleason score. Biopsies of the seminal vesicles are optional.
o Clinical stage T1-T2 on relapse; unilateral extracapsular extension (T3a) on magnetic resonance imaging (MRI) permitted except posteriorly relative to the rectum
o Estimated clinical target volume (CTV) / prostate volume < 0.5 based on imaging and biopsies
o Pelvic and prostatic assessment by multiparametric (mp) MRI
o Absence of pelvic or metastatic recurrence proven by choline positron emission tomography (PET) scan
o Performance status WHO 0-1
o PSA level ≤10 ng/mL at baseline (before salvage-SBRT)
o PSA doubling time >10 months
o IPSS ≤12
o Uroflowmetry with a maximum flow rate >10 mL/s, a postvoid residual urine volume <150 mL, and a urine volume >150 mL.
o No other anti-cancer treatment since the external radiotherapy administered as first-line treatment
o No other anti-cancer treatment planned for the current recurrence
o No contraindication to fiducial marker implants; haemostatic disorders must be corrected before implantation
o Age >18 years
o Life-expectancy greater than or equal to 5 years (Lee scale)
o Patient registered with a health insurance system
o Patient who has signed the informed consent form
o Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests, and other study procedures indicated in the protocol.
EXCLUSION CRITERIA:
o Lymph node or metastatic spread
o Late post-radiotherapy urinary or gastrointestinal toxicity of grade ≥2 (following primary radiotherapy)
o Other cancers in the last 5 years except for non-melanoma-type skin cancer
o History of inflammatory bowel disease
o Anticoagulant treatment
o Contraindications to undergoing MRI
o Prostate volume > 80 cc
o Transurethral resection of the prostate (TURP) in the 6 months before registration
o Presence of rectal telangiectasia grade 3 classified by the Vienne Rectoscopy Score (obligatory rectoscopy) [37,38]
o Previous rectal surgery
o Patients unable to undergo medical follow-up in the study for geographical, social or psychological
o Person deprived of their liberty or under protective

Table 1. Inclusion and exclusion criteria for the study

The phase I primary objective is the selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity observed during the 18 weeks following the initiation of salvage-SBRT. The dose of salvage-SBRT will be selected using a Time-to-Event Continual Reassessment Method (TITE CRM) [34-36] based on dose-limiting toxicity defined as grade ≥3 gastrointestinal or urinary toxicity or any other grade 4 adverse event observed during the 18 weeks following the initiation of salvage-SBRT.

The phase II primary objective is to estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate (Phoenix definition: increase in serum total PSA ≥2 ng/mL above the nadir). Time to bRFS will be computed from registration. Patients alive without biochemical progression at the time of the analysis will be censored at the last follow-up date.

The phase II secondary objectives are:

- Acute and late genitourinary and gastrointestinal toxicities over the first 3 years according to the NCI-CTCAE V4.03 classification (June 14th, 2010), International prostate Symptom Score (IPSS) score for urinary symptoms, and International Index of Erectile Function (IIEF5) for erectile function.
- Quality of life will be evaluated based on the EORTC QLQ-C30 and QLQ-PR25 scales. The Time Until Definitive Deterioration (TUDD) will be computed from registration until the first observation of a definitive deterioration of the quality of life, defined as a score decreased by 10 points (in the case of global health scale and functional scales) or increased by 10 points (in the case of symptom scales) compared to the score at baseline, without later improvement superior to 10 points compared to baseline score.
- Clinical progression-free survival is defined as the time interval between the date of registration and the date of clinical progression (local progression assessed by the physical examination, or appearance of metastatic lesions) or death irrespective of the cause.
- Overall survival is defined as the time interval between the date of registration and the date of death irrespective of the cause.

- Erythroblast transformation-specific related gene (ERG) fusion expression will be evaluated using immunohistochemistry (IHC) tests. ERG fusion and androgen-receptor splice variant 7 (ARV7) expression will be evaluated on biopsies before the first radiotherapy treatment (at diagnosis, if available) and before salvage radiotherapy after biochemical recurrence.

INTERVENTION

A flow chart presenting the different steps from inclusion until treatment is presented in Figure 1. Five or six fractions, at a level of 5 or 6 Gy per session (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy), will be delivered over a maximum of 12 days to provide a total dose of 25 to 36 Gy. This radiotherapy may be administered with the CyberKnife® or a linear accelerator allowing stereotactic radiotherapy. An mpMRI and CT-scan will be carried out at least one week after fiducial implantation. After image transfer to a planimetric console, fiducial-based registration with the prostatic mpMRI will take place in order to provide a better definition of the Gross Target Volume (GTV) and prostatic contours, especially the apex. Multimodality image registration with Choline PET is possible but not mandatory.

Delineation of the target volume will be carried out by a radiotherapist experienced in the definition of prostate volumes on CT-scans and MRIs. GTV will be represented by lesion defined on the mpMRI +/- choline PET; a 5-7 mm margin around the GTV will be used to define the Clinical Target Volume (CTV). CTV is contained in the prostate, except in the case of extracapsular extension (unilateral extracapsular extension on MRI permitted except posteriorly relative to the rectum). In the case where the positive biopsy(ies) are outside and adjacent to the visible lesions on the MRI, the zone containing these biopsies must be included in the CTV so that the prostate cancer recurrence not visible on the MRI is included in the CTV. The total CTV should not be more than half of the total volume of the prostate by MRI. The planning target volume (PTV) will be obtained by an expansion of 2 mm around the CTV in this repeat radiotherapy context. This margin involves that the probability of coverage at 25, 30, or 36 Gy is low, so the reporting will include D2%, 50%, D98% and D95% to describe as much as possible delivered dose.

Quality control is particularly important in this setting of repeat radiotherapy. Before starting patient enrolments a "dummy-run" will be conducted: an anonymous clinical chart will be forwarded to all participating sites with clinical, choline PET-scan, CT-scan and MRI data prior to repositioning. After delineating the relevant volumes, each site will have to perform a dosimetry which will be centralized in order to verify that the constraints are being observed. For each site, the dosimetric data will be subject to a centralized review prior to SBRT administration in order to verify that constraints are being observed. Follow-up visits are described in Figures 1 and 2.

SAMPLE SIZE CALCULATION

Required number of patients to be included: minimum 47 patients. The total sample size will depend upon the number of patients allocated at the different dose levels in the dose-finding parts of the trial. A total of 44 patients allocated at the recommended dose and evaluable at 3 years are required for the main analysis of the Phase II part of the trial to ensure an 85%-power if 3-year bRFS is p1=0.70, with a test against p0=0.50 at a one-sided 5%-alpha level.

STATISTICAL CONSIDERATIONS

PHASE I

Three dose levels of SBRT are to be considered: 5 x 6 Gy, 6 x 6 Gy, and 5 x 5 Gy. The starting dose level is 5 x 6 Gy. A TITE-CRM with an empiric dose-toxicity model in a Bayesian framework will be used for the dose-finding part of the trial to identify the recommended dose. The target dose limiting toxicity (DLT) probability is set at p(DLT)=0.25. Observations of patients who have no DLT at the time of the analysis but have not completed the DLT assessment period will be down-weighted in the likelihood, proportionally to the length of follow up; for instance, if the last patient has been recruited 8 weeks before a new patient is available for enrolment, and is evaluated at week 10 with no DLT, then his observation is attributed a weight of 10/18=0.56.

At least three patients will be enrolled at the first dose-level and fully evaluated over the 18-week study period before the dose is escalated to the next dose-level. Radiation dose levels for further patients will be defined based on the estimate of the probability of DLT at each dose-level considering all available information accumulated so far. Patients will be treated at the best current estimate of the recommended dose i.e. the dose associated with an estimated probability of DLT the closest to the target 0.25. Patients may eventually be treated at a dose below the dose recommended by the model for safety reasons. The patients can be recruited with no minimal time interval between successive inclusions. During the dose-escalation part of the trial, safety data will have to be reported in the data base in real time. Safety data will be discussed with an Independent Data Monitoring Committee (IDMC) at the end of the dose-escalation part of trial, or before if needed.

The dose-escalation part of the study will terminate once 10 patients have been treated and evaluated at a dose currently identified as the recommended dose. Further patients will then be accrued in the expansion cohort, where toxicity data collected over the first 18-week period and DLT assessment will be analyzed approximately every 10 patients with the possibility of modification of the recommended dose, based on model-based estimates.

Specifications of the model are detailed in Appendix, as well as the results of a simulation study evaluating the operating characteristics of the proposed design.

PHASE II

The phase II is based on a one-stage design based on an efficacy endpoint (3-year bRFS). Assuming that information will be available for all patients at 3 years, the endpoint follows a binomial distribution. The design was thus defined considering exact tests, as published by A'Hern.[39] From the literature, the expected bRFS rate at 3 years is approximately 50% in this patient population with various salvage therapies. A 3-year bRFS equal to or lower than 0.50 is deemed insufficient for further evaluation of this approach [p0=0.50]. The considered alternative hypothesis is [p1=0.70].

The Phase II part of the study will need to include 44 patients (including the patients recruited in the dose-finding part of the phase I, allocated at the dose level finally identified as the recommended dose). If all 44 patients are evaluable at 3 years, the treatment strategy will be considered to be insufficiently effective if ≤ 27 patients are alive without a biochemical relapse at 3 years.

The operating characteristics of the design are:

- p0=0.50, p1=0.70
- Defined Type I error = 0.05 (computed type-I error of the design = 0.048)
- Defined Power = 0.85 (computed power = 0.861)

If some patient data are censored before 3 years, the 3-year bRFS will be estimated using Kaplan-Meier method and the lower boundary of the 90% confidence interval will be compared to p0=0.50. The conclusion will be positive if we can reject the null hypothesis p0=0.50 at a one-sided 5% alpha level.

To date, no standard local treatment exists for patients with an intraprostatic recurrence after radiotherapy. A number of treatments options exist including: radical prostatectomy, brachytherapy, HIFU, cryotherapy, and more recently SBRT. These treatments are associated with a variety of genitourinary and gastrointestinal toxicities and complications. The literature to date consists mainly of retrospective and small prospective series making it difficult to assess and compare these techniques. The phase I part of GETUG-AFU 31 trial will evaluate SBRT dose of 30 Gy in 5 fractions, over 12 days, and then depending on tolerance, 36 Gy in 6 fractions over 12 days. The latter, 36 Gy in 6 fractions, is the current scheme used at the Oscar Lambret Centre for all repeat SBRT. This dose is higher than that described by Jereczek-Fossa et al. (30 Gy in 5 fractions),[29] discussed as being too low,[30] but lower than the dose used by Fuller (38 Gy in 4 fractions) [30]. A lower dose (5 x 5 Gy) was used in Zerini et al.[32] We have decided to initially use a phase I study, using dose-limiting toxicity criteria, to establish the best dose (either 5 x 6 Gy, 6 x 6 Gy, or 5 X 5 Gy) for the phase II part of the study. In phase I radiotherapy trials, late complications are often not taken into account and there is currently no consensus on the methodology used for these studies. Although most phase I

radiotherapy studies use a 3+3 design, it is not suitable for these studies as it does not assess late toxicity. More complex designs such as the TITE-CRM are recommended, which will shorten the duration of the entire trial and efficiently uses patient information throughout the study.[40]

Ethics and dissemination

The study has been approved by ethics committee “Ile de France III” (2017-A00008-45) for all study sites.The findings of this study will be disseminated through peer-reviewed publications and conference presentations.

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Declarations

Author Statement

Study Conception: DP. Revision of study design and protocol: DP, MCLD, ET, LC, MD, SN, ERL. Study coordination: DP, MCLD, ET, SN. All authors read and approved the final manuscript.

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Conflicts of interests

The authors declare that they have no competing interests.

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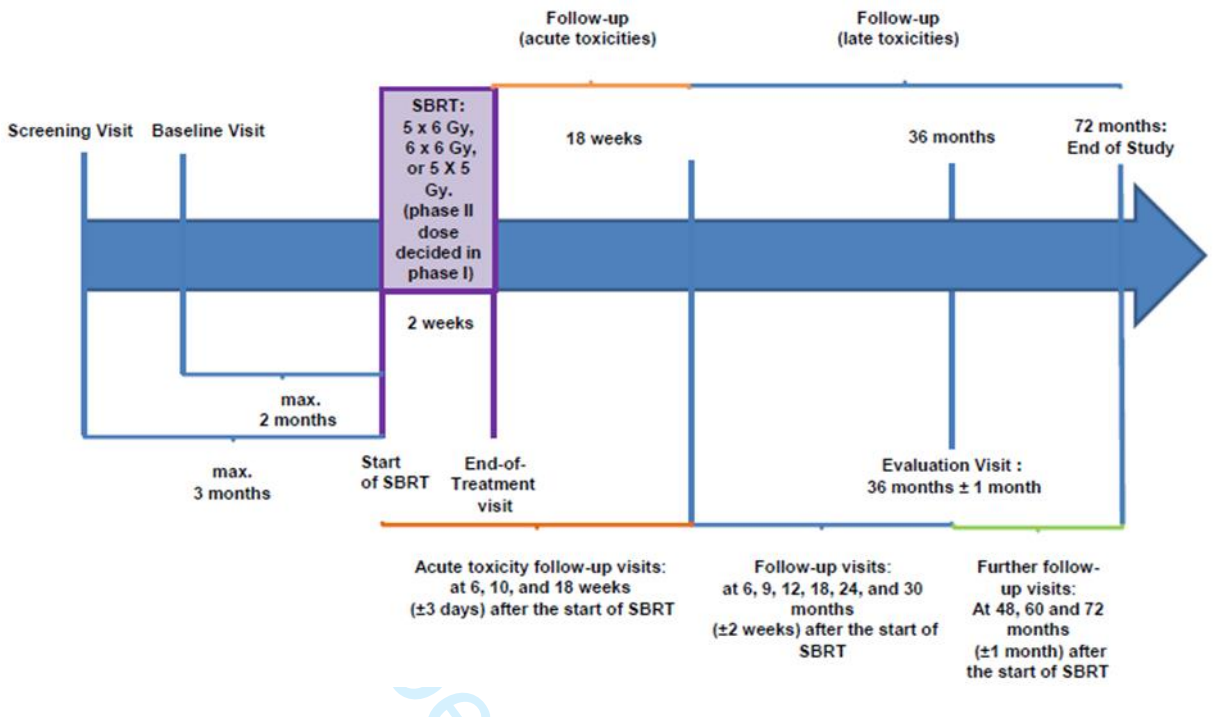
Figures legends

Fig. 1 Overview of study flow chart. SBRT: stereotactic body radiotherapy

Fig 2. Detailed description of study flow chart



	Screening	Baseline	Fiducial placement and treatment planning followed by SALVAGE-SBRT	End of RT visit (at last RT session)	Acute toxicity follow-up visits 6, 10, and 18 weeks (±3 days) after starting SBRT				Follow-up visits 6, 9, 12, 18, 24, and 30 (±2 weeks) after starting SBRT						Evaluation visit 36 months (±1 month) after starting SBRT	Further follow-up visits 48, 60 and 72 months (±1 month) after starting SBRT/End of Study		
Visits	ScV	BV		End RT	W6	W10	W14[1]	W18	M6	M9	M12	M18	M24	M30	M36	M48	M60	M72/End of Study
Eligibility criteria	X	X																
Signed informed consent form	X																	
Enrollment in the study		X																
CLINICAL EXAMINATION																		
Weight, height[4], PS (WHO)	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X
Digital rectal examination (clinical stage)	X	X[5]							X		X	X	X	X	X	X	X	X
Uroflowmetry		X																
Medical history of prostate cancer		X																
Grading of functional digestive, urinary and sexual symptoms (NCI-CTCAE V4.03)		X		X	X	X		X	X	X	X	X	X	X	X	X	X	X
QUESTIONNAIRES																		
QLQ-C30 and QLQ-PR25		X							X		X	X	X	X	X	X	X	X
IPSS		X						X	X		X	X	X	X	X	X	X	X
IIEF5		X						X	X		X	X	X	X	X	X	X	X
LABORATORY TESTS																		
CBC, platelets		X																
PT, PTT, and INR		X																
PSA		X						X		X	X	X	X	X	X	X	X	X
PATHOLOGICAL EVALUATION																		
Gleason score; number of positive biopsies, total number of biopsies; total length of cancer on biopsies; total length of biopsies	X																	
PARACLINICAL INVESTIGATION																		
Multi-parametric MRI (pelvic and prostate)	X[2]								X		X		X		X	X	X	X
Choline PET scan	X[3]																	
TNM evaluation	X																	
TRANSLATIONAL RESEARCH																		
Prostrate tumor biopsies (Initial before any treatment and at recurrence before SBRT)		X[6]																

GETUG-AFU 31: a phase I/II multi-center study evaluating the efficacy of repeat stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation therapy.

Appendix: statistical model, simulation study

Statistical considerations

A TITE-CRM method with an empiric dose-toxicity model in a Bayesian framework will be used for the dose-finding part of the trial to identify the recommended dose. The target dose-limiting toxicity (DLT) probability is set at p(DLT)=0.25. Three dose levels of SBRT are to be considered: 5 x 5 Gy (DL-1), 5 x 6 Gy (DL1), 6 x 6 Gy (DL2). The starting dose level is 5 x 6 Gy and dose level 5 x 5 Gy will be explored in case of DLT at the starting dose level. DLTs are evaluated during the 18 weeks following the initiation of salvage-SBRT. Observations of patients who have no DLT at the time of the analysis but have not completed the DLT assessment period will be down-weighted in the likelihood, proportionally to the length of follow up.

The Phase I part of the study will include 3 patients at the first dose level. Radiation dose levels for further patients will be defined based on the estimate of the probability of DLT at each dose-level considering all available information accumulated so far. Patients will be treated at the best current estimate of the recommended dose i.e. the dose associated with an estimated probability of DLT the closest to the target 0.25. Patients may eventually be treated at a dose below the dose recommended by the model for safety reasons. The patients can be recruited with no minimal time interval between successive inclusions. Two additional rules will be applied during dose escalation: no dose skipping and no escalation if at least 1 DLT is observed in the last 3 patients.
The dose-escalation part of the study will terminate once 10 patients have been treated and evaluated at a dose currently identified as the recommended dose. Further patients will then be accrued in the expansion cohort, where toxicity data collected over the first 18-week period and DLT assessment will be analyzed approximately every 10 patients with the possibility of modification of the recommended dose, based on model-based estimates.
The Phase II part of the study will need to include 44 patients, including the patients recruited in the dose-finding part of the phase I allocated at the dose level finally identified as the recommended dose. Thus, a minimal sample size of 47 patients will be required in this Phase I/II study (in the case of inclusion of 44 patients at dose level 2 + 3 patients at dose level 1).

Statistical model for dose escalation

A one-parameter empirical power model will be used to assess the relation between the dose level and the probability of DLT: $F(d,\alpha) = p_d^{\exp(\alpha)}$ where $F(d,\alpha)$ is the estimated probability of DLT at dose-level d, p_d is the prior probability of DLT at dose level d, and α is the unknown parameter to be estimated by the model. The vector $\{p_{0d}\}$ represent the initial guesses of toxicity probabilities, reflecting the clinicians' prior belief. The skeleton of initial guesses of toxicity probabilities $\{p_{0d}\}$ is numerically calibrated using the Lee and Cheung approach (ref ClinTrials 2009) and using the getprior function of R, ensuring good design's operating characteristics. After discussion with the clinicians, the delta defining the indifference interval was set at 0.05 (p(DLT)=0.25 +/- 0.05, i.e. indifference interval: 0.20 to 0.30) and the prior MTD (MTD_0) at the 2nd dose level, meaning that the clinicians believe, a priori, that the 2nd dose (6 x 6 Gy) is probably the MTD. This yields a vector of prior probabilities $\{p_{0k}\}$ equal to 0.08, 0.16 and 0.25 for dose level -1 (5 x 5Gy), dose level 1 (5 x 6 Gy) and dose level 2 (6 x 6 Gy). The clinicians confirmed that it was in accordance with their initial guesses. A non-informative prior distribution Normal (0, 1.34) has been assigned for α in the Bayesian

computation. The simulation study below confirmed that the operating characteristics and the behavior of the model defined with these parameters were reasonable.

Operating characteristics:

The operating characteristics of the proposed design were evaluated using the R titesim function written by Cheung, and considering six different scenarios:

- highly toxic,
- moderately toxic at dose levels -1 and 1, highly toxic at dose level 2
- moderately toxic et every dose level,
- similar with prior probabilities,
- close to the probabilities but a little less toxic,
- little toxic

For the simulation study, we considered that the trial would recruit 47 patients, which is the minimal sample size required in this Phase I/II study.
The following rules were implemented: no dose skipping in escalation, and no escalation if >1 DLT observed among < 3 patients.
For each case, 1000 trials were simulated. The Monte Carlo estimation of the percentage of dose selection, the average number of patients treated at each dose level, the average number of observed DLTs at each dose level demonstrated that the modified CRM design can efficiently identify the MTD, with a reasonable probability of overdosing, and expose few patients to toxicity.

Figure 1: Scenarios studied

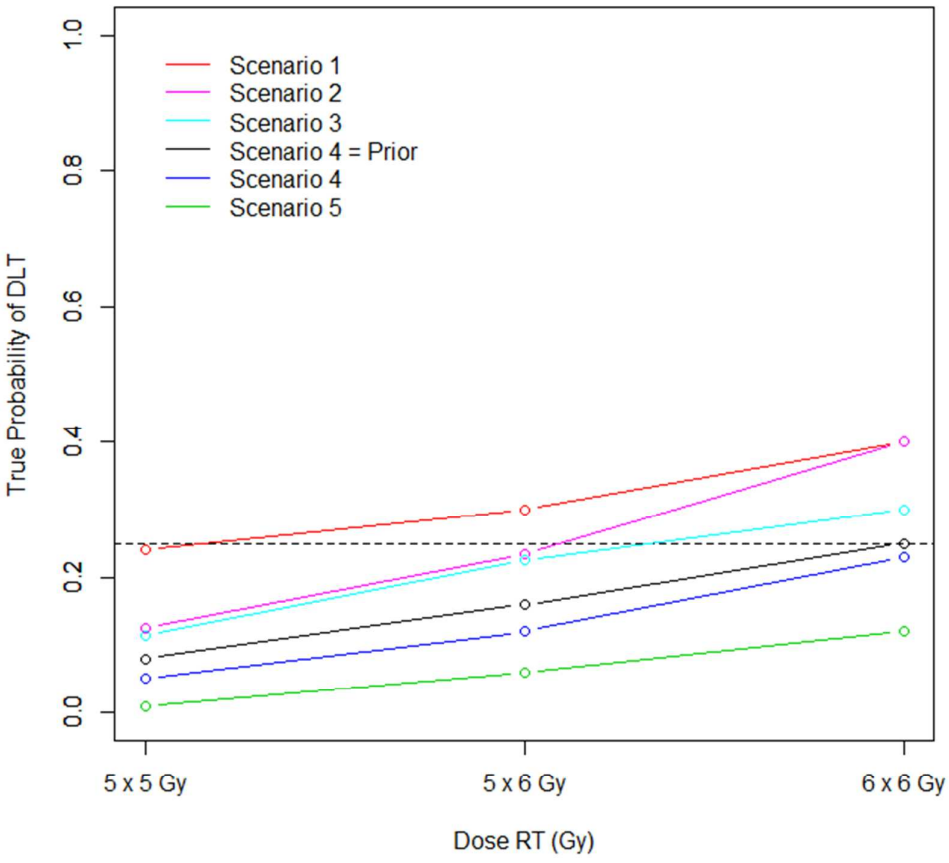


Table 1 : Operating characteristics for five different scenarios for the probability of DLT per dose

The grey row represents the true MTD (proba(DLT) closest to the target of 0.25.

SCENARIO 1 : highly toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT
-1 (5 x 5 Gy)	0.24	0.57	23.7	5.7
1 (5 x 6 Gy)	0.30	0.37	13.4	4.0
2 (6 x 6 Gy)	0.40	0.06	9.9	4.0

Expected number of DLTs over the whole trial (47 patients) = 13.7 / trial

SCENARIO 2: moderately toxic at dose levels -1 and 1, highly toxic at dose level 2

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT
-1 (5 x 5 Gy)	0.12	0.12	10.9	1.3
1 (5 x 6 Gy)	0.23	0.69	21.7	5.1
2 (6 x 6 Gy)	0.40	0.19	14.4	5.8

Expected number of DLTs over the whole trial (47 patients) = 12.1 / trial

SCENARIO 3: moderately toxic at every dose level

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT
-1 (5 x 5 Gy)	0.12	0.08	8.0	1.0
1 (5 x 6 Gy)	0.23	0.52	17.0	3.9
2 (6 x 6 Gy)	0.30	0.40	22.0	6.7

Expected number of DLTs over the whole trial (47 patients) = 11.6 / trial

SCENARIO 4 : true proba(DLT) = prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT
-1 (5 x 5 Gy)	0.08	0.006	3.2	0.3
1 (5 x 6 Gy)	0.16	0.22	11.3	1.8
2 (6 x 6 Gy)	0.25	0.78	32.5	8.2

Expected number of DLTs over the whole trial (47 patients) = 10.3 / trial

SCENARIO 5: little less toxic than prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT
-1 (5 x 5 Gy)	0.05	0.001	2.2	0.1
1 (5 x 6 Gy)	0.12	0.09	8.4	1.0
2 (6 x 6 Gy)	0.23	0.91	36.4	8.4

Expected number of DLTs over the whole trial (47 patients) = 9.5 / trial

SCENARIO 6: little toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT
-1 (5 x 5 Gy)	0.01	0	0.8	0.003
1 (5 x 6 Gy)	0.06	0	2.3	0.1
2 (6 x 6 Gy)	0.12	1.0	43.9	5.3

Expected number of DLTs over the whole trial (47 patients) = 5.4 / trial

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym GETUG AFU 31 Phase I/II Multi-center Study Evaluating the Efficacy of Repeat Stereotactic Radiation in Patients With Intraprostatic Tumor Recurrence After External Radiation Therapy (STEREO-RE-PRO)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ClinicalTrials : NCT03438552
	2b	All items from the World Health Organization Trial Registration Data Set IdRCB : 2017-A00008-45
Protocol version	3	Date and version identifier version n°3.0 – 26/08/2016
Funding	4	Sources and types of financial material, and other support Support by a grant of National Institute of Cancer (INCA)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Docteur David PASQUIER Centre Oscar Lambret - Département de Radiothérapie 3, rue Fréderic Combemale - BP307 59020 Lille Cedex Tél : 03.20.29.59.11 - Fax : 03.20.29.58.96 E-mail : d-pasquier@o-lambret.fr
	5b	Name and contact information for the trial sponsor **UNICANCER** 101 Rue de Tolbiac, 75654 Paris Soazig NENAN +33 (0)185 343 113 s-nenan@unicancer.fr Meryem BRIHOUM +33 (0)1 80 50 12 95 m-brihoum@unicancer.fr

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities None
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention No standard treatment in this setting; to evaluate efficacy and safety of stereotactic body radiotherapy
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses **Primary objective** : Selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity observed during the 18 weeks following the initiation of salvage-SBRT. Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate **Secondary objectives** Evaluation of acute and late genitourinary toxicities of the salvage-SBRT Estimate the efficacy of the salvage-SBRT in terms of clinical progression-free survival and overall survival Evaluation of Quality of life after salvage-SBRT

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Study Type: Interventional ; phase I/II Primary Purpose: Treatment Intervention Model: Sequential Assignment Masking: Open Label Endpoint Classification: Safety/Efficacy Study Enrollment: 47

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Centers are hospitals and clinics (see below) : Centre François Baclesse, Caen, France Principal Investigator: Marlon SILVA Centre Jean Perrin, Clermont-Ferrand, France Principal Investigator: Geneviève LOOS Centre George François Leclerc, Dijon, France Principal Investigator: Gilles CREHANGE Centre Oscar Lambret, Lille, France Principal Investigator: David PASQUIER Centre Léon Bérard, Lyon, France Principal Investigator: Pascal Pommier Institut régional du Cancer de Montpellier, Montpellier, France Principal Investigator: David AZRIA Groupe Hospitalier Pitié-Salpétrière, Paris, France Principal Investigator: Philippe MAINGON ICO -Site René Gauducheau, Saint-Herblain, France Principal Investigator: Stephane SUPIOT Institut de Cancérologie Lucien Neuwirth, Saint-Priest-en-Jarez, France Principal Investigator: Nicolas MAGNE

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

Minimum Age: 18 Years
Gender: Male
Accepts Healthy Volunteers?: No

Inclusion Criteria:

1. Biochemical recurrence occurring at least 2 years after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL)
2. T1-T2c and PSA ≤20 ng/mL and Gleason score ≤7 at initial diagnosis of prostate cancer before the initial/first treatment.
3. Recurrence of prostatic adenocarcinoma proven by histology following radiotherapy by transrectal or transperineal sextant biopsies of the two lobes of the prostate, with a minimum of 12 biopsies, irrespective of Gleason score. Biopsies of the seminal vesicles are optional.
4. Clinical stage T1-T2 on relapse; unilateral extracapsular extension (T3a) on MRI permitted except posteriorly relative to the rectum
5. Estimated clinical target volume (CTV) / prostate volume < 0.5 based on imaging and biopsies
6. Pelvic and prostatic assessment by multiparametric MRI- Absence of pelvic or metastatic recurrence proven by choline PET scan
7. Performance status WHO 0-1
8. PSA level ≤10 ng/mL at baseline (before salvage-SBRT)
9. PSA doubling time >10 months
10. International Prostate Cancer Score (IPSS) ≤12
11. Uroflowmetry with a maximum flow rate >10 mL/s, a postvoid residual urine volume <150 mL, and a urine volume >150 mL.
12. No other anti-cancer treatment since the external radiotherapy administered as first-line treatment
13. No other anti-cancer treatment planned for the current recurrence
14. No contraindication to fiducial marker implants; haemostatic disorders must be corrected before implantation
15. Age >18 years
16. Life-expectancy greater than or equal to 5 years (Lee scale)
17. Patient registered with a health insurance system
18. Patient who has signed the informed consent form
19. Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests, and other study procedures indicated in the protocol.

Exclusion Criteria:

1. Lymph node or metastatic spread
2. Late post-radiotherapy urinary or gastrointestinal toxicity of grade ≥2 (following primary radiotherapy)
3. Other cancers in the last 5 years except for non-melanoma-type skin cancer
4. History of inflammatory bowel disease
5. Anticoagulant treatment
6. Contraindications to undergoing MRI
7. Prostate volume >80 cc
8. Transurethral resection of the prostate (TURP) in the 6 months before registrations
9. Presence of rectal telangiectasia grade 3 classified by the Vienne Rectoscopy Score (obligatory rectoscopy)
10. Previous rectal surgery
11. Patients unable to undergo medical follow-up in the study for geographical, social or psychological
12. Person deprived of their liberty or under protective custody or guardianship
13. Patients enrolled in another therapeutic study

All patients during the SBRT planning with a ratio of clinical target volume (CTV) / prostate volume > 0.5 will be withdrawn from the study. These patients will be considered as not evaluable and will not be treated within the context of the study.

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Focal salvage SBRT (5x6 Gy, 6x6 Gy, 5x5 Gy)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Anticoagulant treatment
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Primary Outcome Measure:** [Time Frame: 18 weeks] Selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity observed during the 18 weeks following the initiation of salvage-SBRT. The dose-escalation part of the study will terminate once 10 patients have been treated and evaluated at a dose currently identified as the recommended dose. [Time Frame: 6 years] Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate **Secondary Outcome Measure:** 1. Time Frame: 3 years] Evaluation of acute and late genitourinary toxicities of the salvage-SBRT 2. [Time Frame: 6 years] Estimate the efficacy of the salvage-SBRT in terms of clinical progression-free survival and overall survival 3. [Time Frame: 6 years] Evaluation of Quality of life after salvage-SBRT
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations 47 patients **Sample Size Calculations:** Required number of patients to be included: minimum 47 patients. The total sample size will depend upon the number of patients allocated at the different dose levels in the dose-finding parts of the trial. A total of 44 patients allocated at the recommended dose and evaluable at 3 years are required for the main analysis of the Phase II part of the trial to ensure an 85%-power if 3-year bRFS is p1=0.70, with a test against p0=0.50 at a one-sided 5%-alpha level.
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Communication and follow-up of the participating centers
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigne
Implementation	16c	Who will generate the allocation sequence: who will enrol participants: and who will assign participants to interventions:
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how Not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Not applicable

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Describe in protocol and data management procedures
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) Not applicable
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Not applicable

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Coordinator : validate the risk analysis (LIR) and the monitoring plan Project Manager : determine the risk analysis (LIR) and write the monitoring plan Clinical Research Associate (CRA) :perform monitoring according the monitoring plan
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct This point is provided by the vigilance unit of the sponsor. All details are described in the protocol
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Actually and according the risk analysis, no audit is planned
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval N° IdRCB : 2017-A00008-45 Initial Approval by CPP Nord-Ouest I (Committee for the Protection of Personnes/Ethic committee) : 25/07/2017 Approval Number: CPP3517-I
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) Each major protocol amendment is submitted to authorities for approval. After approval, it is communicated to all the actors of this project (investigators, trial centers, trial registry ….)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Principal Investigator or sub-investigator
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Collected by investigators and CRA on each trial centers. These data are anonymized. Shared on the eCRF. There is a control access on the eCRF
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site None
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Directly on the eCRF

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions A publication is planned; no publication restriction.
	31b	Authorship eligibility guidelines and any intended use of professional writers Coordinator will be the first author; co investigators will be authors.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code N/A
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

GETUG-AFU 31: a phase I/II multi-center study evaluating the safety and efficacy of salvage stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation therapy; study protocol

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GETUG-AFU 31: a phase I/II multi-center study evaluating the safety and efficacy of salvage stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation therapy; study protocol

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ARTICLE SUMMARY

Introduction. Prostate cancer is the third most important cancer in terms of mortality in men. No standard local treatment exists for patients with an intraprostatic recurrence after radiotherapy. Stereotatic body radiotherapy (SBRT) could be a curative treatment for local recurrence.

Methods and Analysis. We plan to perform a multicenter prospective phase I/II study including at least 47 patients. Eligible patients are patients with biochemical recurrence occurring at least 2 years after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL):

- T1–T2c and PSA ≤20 ng/mL and Gleason score ≤7 at initial diagnosis before the initial/first treatment;
- Recurrence of prostatic adenocarcinoma proven by histology following radiotherapy by transrectal or transperineal sextant biopsies of the two lobes of the prostate, with a minimum of 12 biopsies, irrespective of Gleason score;
- Clinical stage T1-T2 on relapse;
- Pelvic and prostatic assessment by multiparametric MRI;
- Absence of pelvic or metastatic recurrence proven by choline or PSMA PET scan;
- PSA level ≤10 ng/mL at baseline (before salvage-SBRT), PSA doubling time >10 months, IPSS≤12.

The phase I primary objective is the selection of the recommended dose for salvage-SBRT (5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity. The dose of salvage-SBRT will be selected using a Time-to-Event Continual-Reassessment-Method based on dose-limiting toxicity defined as grade ≥3 gastrointestinal or urinary toxicity or any other grade 4 adverse event. The phase II primary objective

is to estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate. Phase II secondary objectives are: acute and late toxicities, quality of life, clinical progression free survival and overall survival.

Ethics and Dissemination. The study has received ethical approval from the Ethics committee "Ile-de-France III". Academic dissemination will occur through publication and conference presentations.

Trial registration: NCT03438552

Date of trial registration: November 14, 2017

Strengths and limitations of this study funding

- Very innovative trial evaluating stereotactic body radiotherapy for recurrent prostate cancer, the only ongoing trial of this kind to our knowledge
- Clinical trial supported by the GETUG-AFU cooperative group, expert in the field, and funded by the French National Cancer Institute (INCa)
- Time-to-Event Continual Reassessment Method, a more appropriate method than the 3+3 design to quantify late toxicity in phase I radiotherapy trials
- Proof-of-concept study; therefore, further research will be required

Keywords: prostate cancer, stereotactic body radiation therapy, recurrent prostate cancer

Background

Prostate cancer is the third most important cancer in terms of mortality in men (after lung and colorectal cancer), and the fourth leading cancer overall [1]. In the European Union, it was predicted that 72600 patients would die from prostate cancer in 2015. The rate of recurrence/relapse of prostate cancer after primary external beam radiotherapy varies from 21% to 65% depending on the study [2,3]. Zelefsky et al. performed biopsies on 339 patients after treatment with 3-dimensional conformal radiotherapy (3D-CRT) or intensity modulated RT for T1c-T3 stage prostate cancer, with a minimum follow-up of 2.5 years [2]. They found that the rate of positive biopsy according to radiation dose was 65% for <70.2 Gy, 38% for 70.2 Gy, 27% for 75.6 Gy, and 25% for ≥81 Gy. A two years biopsy was performed in 312/843 patients included in MRC RT01 trial. A positive biopsy was prognostic of worse biological progression free survival compared with negative and suspicious biopsies, hazard ratio (HR)=4.81 (95% confidence interval [CI]: 2.50-9.26, p<0.001). The estimate for survival was HR=1.58 (95% CI: 0.52-4.78, p=0.42).

In the literature and guidelines a minimum time of two years is recommended between radiotherapy and prostate biopsies to minimize the risk of false positive and this two-year interval has been selected in our study. This risk decreases over time. Nevertheless the guidelines recommend to perform prostate biopsies before any salvage treatment, and the diagnosis is based on imaging too in our study.

D'Amico reported that the 5-year prostate cancer mortality rate after biochemical recurrence in patients who received external beam radiotherapy for localized prostate cancer depended on the pretreatment Gleason score: 24% for ≤6 score, 40% for 3+4 score, and 59% for 4+3 or higher score (p=0.01); as well as, on the pretreatment PSA level: 22% for ≤10 ng/mL, 40% for >10 and ≤20 ng/mL, and 60% for >20 ng/mL (p=0.04) [4]. In addition, Buyyounouski reported that the interval to biochemical recurrence was an important factor in identifying men at high risk of distant metastasis and death [5]. An interval to biochemical recurrence (PSA nadir + 2 ng/mL) of <18 vs. ≥18 months was associated with a 5-year distant metastasis rate of 52% vs. 20% (p<0.0001), and a prostate-cancer

specific mortality rate of 36% vs. 6% (p=0.0001). Thus late relapse and long PSA doubling time are prognostic factors of solely intraprostatic relapse.

Prostate-specific antigen (PSA) is a validated biomarker for prostate cancer. PSA levels are extensively used to monitor response to radical prostatectomy (RP) and external-beam radiotherapy (EBRT). The serum PSA level is an important surrogate for recurrence in prostate cancer patients. The recommendations of the Radiation Therapy Oncology Group (RTOG) ASTRO Phoenix Consensus Conference suggested that an increase of ≥2 ng/mL from the nadir be used to define recurrence/relapse [6]. It is important to note that biochemical recurrence may indicate local or systemic disease recurrence, and may require prostate biopsy for confirmation particularly when local salvage treatments are being considered [7].

A number of different salvage treatments have been used after failure of primary radiotherapy. RP is more invasive than brachytherapy, ultrasound, high-intensity focused ultrasound (HIFU), and SBRT. Below is a brief discussion of the results obtained with each techniques and its associated toxicity and complications.

Salvage RP (SRP) is a treatment option after local recurrence following EBRT. However, the morbidity, including incontinence and erectile dysfunction, is higher than that observed with first-line RP patients. A systematic literature review [7] reported that the probability of biochemical relapse–free survival (bRFS) following SRP in prostate cancer patients was 47-82% after 5 years and 28-53% after 10 years. SRP has an increased risk of adverse events due to fibrosis and poor wound healing after radiotherapy. Furthermore, SRP after radiotherapy compared to primary RP has a significantly higher rate of urinary and gastrointestinal morbidity [8]. The review above [7], reported that the most frequent complications were anastomotic stricture (7-41%) and rectal injury (0-28%). The majority (50-91%) of men had erectile dysfunction before SRP and 80-100% after surgery. Post-operative urinary continence ranged from 21-90%.

In a recent review, salvage brachytherapy after EBRT is reported to achieve biochemical control rates of 20% to 89% (median follow-up: 19 to 108 months) [9]. Rates of genitourinary toxicities range

from 12% to 87% for grade 1-2, and 3% to 47% for grade 3-4 toxicities. Similarly, the rates of gastrointestinal toxicities range from 4% to 65% for grade 1-2, and 0% to 20% for grade 3-4 toxicities. Erectile dysfunction was observed in 2% to 95% of men. A phase II study of salvage high-dose-rate brachytherapy (HDR) for treating recurrent prostate cancer after definitive external beam radiotherapy was reported by Yamada [10]. The 42 patients enrolled, with biopsy proven recurrence, were treated with salvage HDR (iridium-192) with a resulting bRFS at 5 years of 68.5% (median follow-up of 36 months [range: 2-66 months]). Acute genitourinary toxicity was observed: grade 1, 38% of patients and grade 2: 40%. Similarly, late genitourinary toxicity was observed: grade 1, 38% of patients and grade 2, 48%. In addition, 1 patient had a grade 3 urinary incontinence and 3 had grade 3 urethral strictures. Late gastrointestinal toxicities were observed: grade 1, 43% of patients and grade 2, 14%. More recently, a study of 83 prostate cancer patients with local recurrence after radiotherapy treated with high-dose-rate brachytherapy was reported [11]. The 3-year and 5-year bRFS were 76% and 67%. A phase II study of the RTOG in 100 patients was recently presented: twelve (14%) experienced late grade 3 genitourinary/gastrointestinal adverse effects. This rate of late grade 3 toxicity (14%) was not unacceptable by the predetermined protocol specification, without any grade 4-5 events. The only factor predictive of late toxicity was implant dose, underlining the need for meticulous planning and technique to limit the final delivered dose [12]. In France, a phase II study, “Brachytherapy for Recurrent Prostate Cancer” (CAPRICUR) was recently completed [13].

HIFU is another less invasive salvage treatments following recurrence. HIFU uses focused ultrasound to generate heat (85°C) which induces tissue necrosis [14]. The following studies have investigated the use of salvage-HIFU after initial radiotherapy. A French group treated 290 men with biopsy-confirmed recurrent prostate cancer, after radiotherapy, with salvage HIFU [15]. At 7 years, the cancer-specific survival rate was 80% and the metastasis-free survival rate was 79.6%. Recto-urethral fistula occurred in 0.4% of patients and 19.5% had grade 2/3 incontinence. Half of the patients also received hormone therapy. Survival without relapse at 5 years after HIFU, by D’Amico risk groups prior to their initial treatment, was 45% (favorable), 31% (intermediate risk) and 21%

(high risk). In this cohort, the grade ≤3 urinary incontinence levels were 23% (favorable), 14% (intermediate risk) and 9% (high risk). Nearly 8% of patients required an artificial sphincter following HIFU. Importantly, pubic osteitis occurred in 2.5% of patients despite adherence to parameters specific to HIFU following radiotherapy [15].

Cryotherapy is thermo-ablative treatment; the third–generation argon/helium-based cryotherapy system creates precise isotherms through ultrathin needles [16]. In a retrospective multicenter series pooling 279 patients, survival without biochemical relapse at 5 years was 54%. Prostatic biopsies showed tumor persistence in 32% of patients following cryotherapy [17]. In a paired case-controlled study, prostatectomy and cryotherapy were compared following radiotherapy. Survival without relapse (PSA nadir + 0.4 ng/mL) at 5 years was significantly lower after cryotherapy (21% vs. 61%, p<0.001); this was confirmed by the 5-year OS rate of 85%, cryotherapy, vs 95%, radical prostatectomy (p=0.001) [18]. Intermediate results from a study investigating third-generation cryotherapy as a salvage treatment of locally recurrent prostate cancer after radiotherapy was published [19]. The 5-year bRFS rate (Phoenix definition) was 43.5% and with a 5-year OS rate of 92.3%. Mild complications (grades 1 and 2) were reported including: mild incontinence (9.4%), acute rectal pain (31.3%), lower urinary tract symptoms (15.6%) and erectile dysfunction (57.1%). Grade 3 toxicities: incontinence (3.1%) and urethral sloughing (3.1%) were observed.

Androgen-deprivation therapy (ADT) alone (continuous or intermittent) is commonly given to patients with biochemical relapse after radiotherapy [20]. In a series based on data from a North American national registry (CaPSURE), 71% of patients were treated for biochemical relapse after prostatectomy or radiotherapy. ADT was initiated in 93% of these patients, and the remaining patients were treated with surgery, brachytherapy, cryotherapy, or repeat external radiotherapy [21]. ADT may cause adverse effects impacting patient's quality of life (including: hot flushes, erectile dysfunction and reduced libido, cognitive impairment, and anemia). The metabolic changes associated with hormone therapy may also increase the risk of cardiovascular morbidity. The reduction in bone mass is maximal in the first year and increases with the duration of castration; the

risk of fracture is increased in patients surviving for more than 5 years [22-23]. The guidelines suggest that a simple follow-up can be implemented for local recurrence in patients with a limited life expectancy or for those who do not wish to undergo local salvage treatment. The last European Association of Urology guidelines [24] recommended to perform salvage surgery in experienced centres due to the increased rate of side effects. It is recommended to offer/discuss HIFU, cryosurgical ablation and salvage brachytherapy to/with patients without evidence of metastasis and with histologically proven local recurrence and to inform patients about the experimental nature of these approaches. The level of evidence for each of these recommendations is 3 [24].

SBRT delivers highly conformal, high-dose radiation in a few fractions (hypofractionation), typically 5 to 7 fractions for prostate cancer. It is reported that tissues with a low α/β ratio, as for prostate cancer, are more sensitive to large doses of radiation per fraction. The surrounding normal tissue could have similar or higher α/β ratio. This suggests that hypofractionation (large radiation dose per fraction) may result in improved tumor control with limited toxicity. A pooled analysis of 1100 patients included in separate prospective phase II studies in 8 institutions was performed to evaluate the effectiveness of SBRT as a first-line treatment for localized prostate cancer [25]. The SBRT was delivered by CyberKnife with a median dose of 36.25 Gy in 4-5 fractions. The 5-year bRFS rate was 93% for all patients. Thus relapse-free survival rates after SBRT compare favourably with other definitive treatments for low and intermediate-risk patients with a short follow up. SBRT is well tolerated with a low effect on quality of life [25-28]. In addition sexual function appeared to be spared in the majority of patients [25-28].

SBRT has also been used as a salvage treatment following failure of external radiotherapy. Jereczek-Fossa et al. published data on 34 consecutive patients treated with robotic SBRT for isolated recurrent primary, lymph node, or metastatic prostate cancer [29]. Of the 34 patients, 15 patients had intraprostatic recurrence, confirmed by biopsy, and were treated with SBRT (CyberKnife) with a median dose of 30 Gy in 5 fractions. Fourteen patients showed a biochemical response; the median survival without recurrence was 13 months. Five patients presented a clinical relapse, including one

new intraprostatic recurrence. Urinary toxicity was low, with a grade 3 urinary toxicity in only one patient. No case of acute or late gastrointestinal toxicity was reported. This good gastrointestinal tolerability has subsequently been confirmed [29-32]. In Fuller et al twenty-nine patients were treated in a phase II trial with stereotactic radiotherapy for intraprostatic recurrence [30]. Eligible patients had to present biopsy-proven intraprostatic recurrence graded T1 to T3N0M0 more than 2 years post-radiotherapy and without a pre-existing grade >1 radiotherapy toxicity. The prior median dose delivered was 73.8 Gy and the median interval between the treatments was 88 months. The dose delivered to the entire gland was 34 Gy in five fractions over 5 days (heterogeneous intraprostatic dose of up to 50 Gy). With a median follow-up of 24 months, survival without recurrence was 82%. Toxicity was acceptable, with 18% grade ≥2 urinary toxicity, including one patient with a grade 4 toxicity, and no late gastrointestinal toxicity above grade 1. Particular attention should be given to patients who still exhibit urinary toxicity after initial radiotherapy [30]. Our preliminary retrospective results in 23 patients treated for this indication were published recently [31]. A total dose of 36 Gy was prescribed in 6 fractions of 6 Gy. Nineteen patients had a whole-gland and four a partial treatment. Median follow-up was 23 months (range 6 to 40 months). We observed no grade 4 or 5 toxicity. Two patients presented grade 3 toxicities. Others toxicities include urinary (5 grade 2 and 9 grade 1) and rectal toxicities (2 grade 2 and 2 grade 1). The dose levels selected in our study are close to those used in de novo patients, and the same as those described in retrospective salvage treatment series. These schemes seem to provide an acceptable compromise between efficacy and toxicity but have not been evaluated prospectively.

To date, no standard local treatment exists for patients with an intraprostatic recurrence after radiotherapy [33]. A number of treatments options exist including: radical prostatectomy, brachytherapy, HIFU, cryotherapy, and stereotactic radiotherapy. The literature to date consists mainly of retrospective and small prospective series making it difficult to assess and compare these techniques. In recent years, SBRT has been used to treat localized prostate cancer in the primary setting but also as a salvage treatment after failure of radiotherapy. The initial results of these

retrospective studies are promising, with respect to survival and tolerance, but further studies are required to confirm these initial results. Our proposed study will provide further evidence of SBRT as a supplementary non-invasive curative treatment for local recurrence following radiotherapy. This study could provide the foundation for prospective studies comparing the available salvage treatments after radiotherapy.

Methods/design

This study is approved by the Ethics committee "Ile de France III" (2017-A00008-45) and is registered on clinicaltrials.gov (NCT03438552). This multicenter open-labelled phase I/II study will initially select the SBRT scheme (phase I), either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy. The effectiveness of SBRT scheme selected in phase I will then be evaluated in a single-arm multicenter phase II study.

PHASE I primary objective and assessment:

Selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity observed during the 18 weeks following the initiation of salvage-SBRT. The dose of salvage-SBRT will be selected using a Time-to-Event Continual Reassessment Method [34-36] based on dose-limiting toxicity defined as grade ≥3 gastrointestinal or urinary toxicity or any other grade 4 adverse event observed during the 18 weeks following the initiation of salvage-SBRT.

PHASE II primary objective and assessment:

Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate (Phoenix definition: increase in serum total PSA ≥2 ng/mL above the nadir). Time to biochemical relapse-free survival will be computed from registration. Patients alive without biochemical progression at the time of the analysis will be censored at the last follow-up date. In the event of death, whatever the cause of death, the patient will be considered as a failure.

PHASE II secondary objective(s) and assessment:

- Acute and late genitourinary and gastrointestinal toxicities over the first 3 years according to the NCI-CTCAE V4.03 classification (June 14th, 2010), International prostate Symptom Score (IPSS) score for urinary symptoms, and International Index of Erectile Function (IIEF5) for erectile function. Patients will be followed for 5 years after salvage SBRT to assess late toxicity. Patients with second biochemical recurrence will not be excluded in order to assess late toxicity.
- Quality of life will be evaluated based on the EORTC QLQ-C30 and QLQ-PR25 scales. The Time Until Definitive Deterioration (TUDD) will be computed from registration until the first observation of a definitive deterioration of the quality of life, defined as a score decreased by 10 points (in the case of global health scale and functional scales) or increased by 10 points (in the case of symptom scales) compared to the score at baseline, without later improvement superior to 10 points compared to baseline score.
- Clinical progression-free survival is defined as the time interval between the date of registration and the date of clinical progression (local progression assessed by the physical examination, or appearance of metastatic lesions) or death irrespective of the cause.
- Overall survival is defined as the time interval between the date of registration and the date of death irrespective of the cause.
- Erythroblast transformation-specific related gene (ERG) fusion expression will be evaluated using immunohistochemistry (IHC) tests. ERG fusion and androgen-receptor splice variant 7 (ARV7) expression will be evaluated on biopsies before the first radiotherapy treatment (at diagnosis, if available) and before salvage radiotherapy after biochemical recurrence.

DIAGNOSIS AND INCLUSION CRITERIA:

- Biochemical recurrence occurring at least 2 years after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL)

- T1–T2c and PSA ≤20 ng/mL and Gleason score ≤7 at initial diagnosis of prostate cancer before the initial/first treatment.
- Recurrence of prostatic adenocarcinoma proven by histology following radiotherapy by transrectal or transperineal sextant biopsies of the two lobes of the prostate, with a minimum of 12 biopsies, irrespective of Gleason score. Biopsies of the seminal vesicles are optional.
- Clinical stage T1-T2 on relapse; unilateral extracapsular extension (T3a) on magnetic resonance imaging (MRI) permitted except posteriorly relative to the rectum
- Estimated clinical target volume (CTV) / prostate volume < 0.5 based on imaging and biopsies
- Pelvic and prostatic assessment by multiparametric (mp) MRI
- Absence of pelvic or metastatic recurrence proven by choline positron emission tomography (PET) scan
- Performance status WHO 0-1
- PSA level ≤10 ng/mL at baseline (before salvage-SBRT)
- PSA doubling time >10 months
- IPSS ≤12
- Uroflowmetry with a maximum flow rate >10 mL/s, a postvoid residual urine volume <150 mL, and a urine volume >150 mL.
- No other anti-cancer treatment since the external radiotherapy administered as first-line treatment
- No other anti-cancer treatment planned for the current recurrence
- No contraindication to fiducial marker implants; haemostatic disorders must be corrected before implantation
- Age >18 years

- Life-expectancy greater than or equal to 5 years (Lee scale)
- Patient registered with a health insurance system
- Patient who has signed the informed consent form
- Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests, and other study procedures indicated in the protocol.

EXCLUSION CRITERIA:

- Lymph node or metastatic spread
- Late post-radiotherapy urinary or gastrointestinal toxicity of grade ≥2 (following primary radiotherapy)
- Other cancers in the last 5 years except for non-melanoma-type skin cancer
- History of inflammatory bowel disease
- Anticoagulant treatment
- Contraindications to undergoing MRI
- Prostate volume > 80 cc
- Transurethral resection of the prostate (TURP) in the 6 months before registration
- Presence of rectal telangiectasia grade 3 classified by the Vienne Rectoscopy Score (obligatory rectoscopy) [37,38]
- Previous rectal surgery
- Patients unable to undergo medical follow-up in the study for geographical, social or psychological
- Person deprived of their liberty or under protective

INTERVENTION

A flow chart presenting the different steps from inclusion until treatment is presented in Fig. 1. Five or six fractions, at a level of 5 or 6 Gy per session (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy), will be delivered over a maximum of 12 days to provide a total dose of 25 to 36 Gy. This radiotherapy may

be administered with the CyberKnife® or a linear accelerator allowing stereotactic radiotherapy. The patient will be placed in a stable and reproducible supine position. Intraprostatic markers (fiducials) will be implanted before the dosimetric CT-scan and MRI are performed. The choice of markers is left to the discretion of each participating site (gold seeds, etc.). The site needs to ensure that the repositioning of the prostate is precise (≤2 mm), allowing an exact overlay between dosimetric MRI and computed tomography (CT)-scan. The implant of fiducials is obligatory irrespective of the stereotactic radiotherapy technique used. The fiducials can be implanted during or after the biopsies. The CT-scans and MRIs registration is guided by the fiducials. Each team can choose the fiducials visible on the MRI they wish to use and/or integrate a specific sequence during the centering MRI for better visualization.

An mpMRI and CT-scan will be carried out at least one week after fiducial implantation. CT-scan images should be acquired with the patient in the treatment position using the chosen immobilizing system, if required according to centers' standard procedures. An intravenous injection of a contrast product should be administered unless contraindicated. Acquisition should allow anatomical structures and markers (already implanted in the prostate) to be visualized. The bladder will be half-filled (neither full nor empty, i.e. a final voiding 90 minutes before the CT-scan followed by ingestion of 250-350 mL of water). The rectum will be empty and not distended. If necessary rectal enema can be used before CT-scan acquisition. Contiguous CT-scan slices ≤2 mm thick will be taken between the L5-S1 joint space and the small trochanters. After image transfer to a planimetric console, fiducial-based registration with the prostatic mpMRI will take place in order to provide a better definition of the Gross Target Volume (GTV) and prostatic contours, especially the apex. Fiducial-based CT-MRI registration is mandatory. Multimodality image registration with Choline PET is possible but not mandatory.

Delineation of the target volume will be carried out by a radiotherapist experienced in the definition of prostate volumes on CT-scans and MRIs. The mpMRI-defined contour will be integrated with the CT-scan derived contours in order to define tumor and the prostatic apex more precisely.

GTV will be represented by lesion defined on the multiparametric MRI +/- choline PET; a 5-7 mm margin around the GTV will be used to define the Clinical Target Volume (CTV). CTV is contained in the prostate, except in the case of extracapsular extension (unilateral extracapsular extension on MRI permitted except posteriorly relative to the rectum). In the case where the positive biopsy(ies) are outside and adjacent to the visible lesions on the MRI, the zone containing these biopsies must be included in the CTV so that the prostate cancer recurrence not visible on the MRI is included in the CTV. If no lesion is visible on the MRI and/or choline PET, the zone containing positive biopsies must be included in the CTV. For example: MRI +/-choline PET lesion in 3p and 4p according to ESUR guidelines, with positive biopsies in 1p, 3p and 4p: CTV = MRI GTV + 5 mm + the posterior right base. The total CTV should not be more than half of the total volume of the prostate by MRI. The planning target volume (PTV) will be obtained by an expansion of 2 mm around the CTV in this repeat radiotherapy context. This margin involves that the probability of coverage at 25, 30, or 36 Gy is low, so the reporting will include D2%, 50%, D98% and D95% to describe as much as possible delivered dose. Organs at risk constraints are specified in Table 1. Daily image guided radiation therapy is mandatory, intra fraction tracking is recommended.

Rectum	Bladder	Urethra + 3 mm
V27 Gy <2 cc	V27 Gy <5 cc	V24 Gy <30%
V12 Gy <20%	V12 Gy <15%	D_{max} (35 mm^3) <39 Gy
		V36 Gy <1 cc

Table 1. Organs at risk constraints

Quality control is particularly important in this setting of repeat radiotherapy. Before starting patient enrolments a “dummy-run” will be conducted: an anonymous clinical chart will be forwarded to all participating sites with clinical, scintigraphy (choline PET-scan), CT-scan and MRI data prior to repositioning. After delineating the relevant volumes, each site will have to perform a dosimetry

which will be centralized in order to verify that the constraints are being observed. For each site, the dosimetric data will be subject to a centralized review prior to SBRT administration in order to verify that constraints are being observed. Follow-up visits are described in Figures 1 and 2.

SAMPLE SIZE CALCULATION

Required number of patients to be included: minimum 47 patients. The total sample size will depend upon the number of patients allocated at the different dose levels in the dose-finding parts of the trial. A minimum of 13 patients will be recruited before the expansion phase is open (Phase II part). A total of 44 patients allocated at the recommended dose (recruited in the dose-escalation stage or in the expansion phase) and evaluable at 3 years are required for the main analysis of the Phase II part of the trial to ensure an 85%-power if 3-year bRFS is p1=0.70, with a test against p0=0.50 at a one-sided 5%-alpha level.

STATISTICAL CONSIDERATIONS

PHASE I

Three dose levels of SBRT are to be considered: 5 x 6 Gy, 6 x 6 Gy, and 5 x 5 Gy. The starting dose level is 5 x 6 Gy. The lower dose level, 5 x 5 Gy, will be considered if excessive toxicity is reported at the first dose-level (5 x 6 Gy). A TImeTo Event-Continuous Reassessment Method (TITE-CRM) with an empiric dose-toxicity model in a Bayesian framework will be used for the dose-finding part of the trial to identify the recommended dose. The target dose limiting toxicity (DLT) probability is set at p(DLT)=0.25. Observations of patients who have no DLT at the time of the analysis but have not completed the DLT assessment period will be down-weighted in the likelihood, proportionally to the length of follow up; for instance, if the last patient has been recruited 8 weeks before a new patient is available for enrolment, and is evaluated at week 10 with no DLT, then his observation is attributed a weight of 10/18=0.56.

At least three patients will be enrolled at the first dose-level and fully evaluated over the 18-week study period before the dose is escalated to the next dose-level. Radiation dose levels for further patients will be defined based on the estimate of the probability of DLT at each dose-level considering all available information accumulated so far. Patients will be treated at the best current estimate of the recommended dose i.e. the dose associated with an estimated probability of DLT the closest to the target 0.25. Patients may eventually be treated at a dose below the dose recommended by the model for safety reasons. The patients can be recruited with no minimal time interval between successive inclusions. During the dose-escalation part of the trial, safety data will have to be reported in the data base in real time. A monthly teleconference meeting with the participation of the biostatistician, the trial coordinator and a representative of the sponsor, to summarize toxicity observations and define the dose to be allocated to the next patient(s) will be held. Safety data will be discussed with an Independent Data Monitoring Committee (IDMC) at the end of the dose-escalation part of trial, or before if needed.

The dose-escalation part of the study will terminate once 10 patients have been treated and evaluated at a dose currently identified as the recommended dose. Further patients will then be accrued in the expansion cohort, where toxicity data collected over the first 18-week period and DLT assessment will be analyzed approximately every 10 patients with the possibility of modification of the recommended dose, based on model-based estimates.

Specifications of the model are detailed in appendix, as well as the results of a simulation study evaluating the operating characteristics of the proposed design.

PHASE II

The phase II is based on a one-stage design based on an efficacy endpoint (3-year bRFS). Assuming that information will be available for all patients at 3 years, the endpoint follows a binomial distribution. The design was thus defined considering exact tests, as published by A'Hern [39].

From the literature, the expected bRFS rate at 3 years is approximately 50% in this patient population with various salvage therapies. A 3-year bRFS equal to or lower than 0.50 is deemed insufficient for further evaluation of this approach [p0=0.50]. The considered alternative hypothesis is p1=0.70].

The Phase II part of the study will need to include 44 patients (including the patients recruited in the dose-finding part of the phase I, allocated at the dose level finally identified as the recommended dose). If all 44 patients are evaluable at 3 years, the treatment strategy will be considered to be insufficiently effective if ≤ 27 patients are alive without a biochemical relapse at 3 years.

The operating characteristics of the design are:

- p0=0.50, p1=0.70
- Defined Type I error = 0.05 (computed type-I error of the design = 0.048)
- Defined Power = 0.85 (computed power = 0.861)

If some patient data are censored before 3 years, the 3-year bRFS will be estimated using Kaplan-Meier method and the lower boundary of the 90% confidence interval will be compared to p0=0.50. The conclusion will be positive if we can reject the null hypothesis p0=0.50 at a one-sided 5% alpha level.

PATIENT AND PUBLIC INVOLVEMENT

Patients were not involved in the idea conception of this trial.

Patients were not involved in the design of this study nor in recruitment of the study.

Discussion

To date, no standard local treatment exists for patients with an intraprostatic recurrence after radiotherapy. A number of treatments options exist including: radical prostatectomy, brachytherapy, HIFU, cryotherapy, and more recently SBRT. These treatments are associated with a variety of genitourinary and gastrointestinal toxicities and complications. The literature to date consists mainly

of retrospective and small prospective series making it difficult to assess and compare these techniques. Philippou et al compared oncologic and toxicity outcomes of SRP versus nonsurgical therapies except SBRT with a meta-regression analysis. Oncologic and toxicity outcomes appear to be similar; however, all nonsurgical salvage modalities may be associated with better continence outcomes [40].

The sensitivity of PSMA-PET is higher than that of choline-PET for the detection of lymph node disease [41]. Unfortunately PSMA PET is not routinely available in France. A modification of the inclusion criteria is being drafted to allow PSMA PET if this examination becomes available during the study period. To have a high sensitivity, a lymph node staging must be extensive, which can have side effects in this context. Furthermore clinical and biological selection criteria (no high risk cancer before first treatment, PSA level, PSA doubling time,...) are designed to select the patients to have most likely intra-prostatic recurrence only.

The phase I part of GETUG-AFU 31 trial will evaluate SBRT dose of 30 Gy in 5 fractions, over 12 days, and then depending on tolerance, 36 Gy in 6 fractions over 12 days. The latter, 36 Gy in 6 fractions, is the current scheme used at the Oscar Lambret Centre for all repeat SBRT. This dose is higher than that described by Jereczek-Fossa et al. (30 Gy in 5 fractions) [29], discussed as being too low [30], but lower than the dose used by Fuller (38 Gy in 4 fractions) [30]. A lower dose (5 x 5 Gy) was used in Zerini et al [32]. We have decided to initially use a phase I study, using dose-limiting toxicity criteria, to establish the best dose (either 5 x 6 Gy, 6 x 6 Gy, or 5 X 5 Gy) for the phase II part of the study. In phase I radiotherapy trials, late complications are often not taken into account and there is currently no consensus on the methodology used for these studies. Although most phase I radiotherapy studies use a 3+3 design, it is not suitable for these studies as it does not assess late toxicity. More complex designs such as the TITE-CRM are recommended, which will shorten the duration of the entire trial and efficiently uses patient information throughout the study [42].

Abbreviations

GETUG-AFU: “Groupe d’Etude des Tumeurs Uro Genitales- Association Française d’Urologie”; PSA: prostate-specific antigen; RP: radical prostatectomy; EBRT: external-beam radiotherapy; SBRT: stereotactic body radiation therapy; HIFU: high-intensity focused ultrasound; bRFS: biochemical relapse–free survival; HDR: high dose rate; RTOG: radiation therapy oncology group; ADT: androgen-deprivation therapy; CTCAE: common toxicity criteria adverse events; Gy: Gray; TITE-CRM: Time-to-Event Continual Reassessment Method; IIEF: International Index of Erectile Function; CTV: clinical target volume; PTV: planning target volume; QOL: Quality of life; RTOG: Radiation Therapy Oncology Group; TUDD: time until definitive deterioration; ERG: Erythroblast transformation-specific related gene; IHC: immunohistochemistry; ARV7: Androgen-receptor splice variant 7; MRI: magnetic resonance imaging; TURP: transurethral resection of the prostate; CT: computed tomography; mpMRI: multiparametric MRI; PET: positron emission tomography; WHO: world health organization; GTV: gross tumor volume; DLT: dose limiting toxicity

Declarations

Ethics approval and consent to participate

The study has been submitted and approved by ethics committee (the ethical committee “Ile de France III” (2017-A00008-45) for all study sites. The study opened in February 2018.
A written informed consent will be obtained from the study participants.
There is an agreement between each participating center and Unicancer. Each protocol version is signed by the principal investigator. We have a copy of each signed document.
In France, according to the current law, a protocol can be subjected to any regional Ethics Committee, even if no hospital of this region takes part to the trial. The choice is made according to the workload of every committee. The opinion of this Ethics Committee applies to all the national centers.

Consent for publication

A signed informed consent is obtained from all patients included in the trial.

Availability of data and material

The data set used and/or analysed during the current study are available from the corresponding author on reasonable request. Not all data are obtained yet since the study is still ongoing.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Study Conception: DP. Revision of study design and protocol: DP, MCLD, ET, LC, MD, SN, ERL. Study coordination: DP, MCLD, ET, SN. All authors read and approved the final manuscript.

Acknowledgments

None

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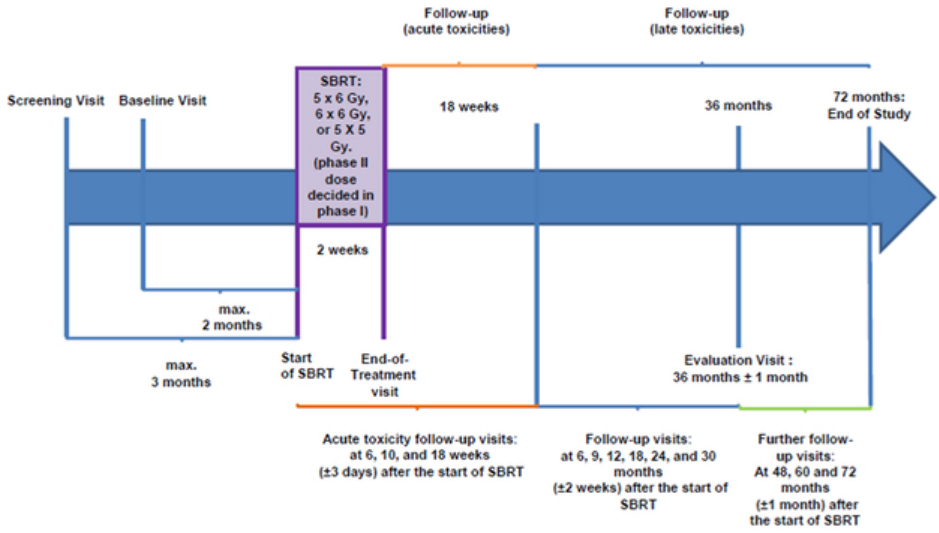
Figures legends

Fig. 1 Overview of study flow chart. SBRT: stereotactic body radiotherapy

Fig 2. Detailed description of study flow chart.

(1.Patient will be contacted by phone 14 weeks after starting SBRT to assess toxicity; an additional visit may be scheduled if required; 2 .Before inclusion, during regular follow-up and in case of biochemical recurrence after SBRT; 3 .Before inclusion and in case of biochemical recurrence after SBRT; 4.Patient's height will only be measured at the screening visit; 5. If not done at the screening visit.; 6.Only applicable for patients who have consented to participate in the biological ancillary study)



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	Screening	Baseline		End of RT visit (at last RT session)	Acute toxicity follow-up visits 6, 10, and 18 weeks (±3 days) after starting SBRT				Follow-up visits 6, 9, 12, 18, 24, and 30 (±2 weeks) after starting SBRT						Evaluation visit 36 months (±1 month) after starting SBRT	Further follow-up visits 48, 60 and 72 months (±1 month) after starting SBRT/End of Study		
Visits	**ScV**	**BV**		**End RT**	**W6**	**W10**	**W14[1]**	**W18**	**M6**	**M9**	**M12**	**M18**	**M24**	**M30**	**M36**	**M48**	**M60**	**M72/End of Study**
Eligibility criteria	X	X	Fiducial placement and treatment planning followed by SALVAGE-SBRT															
Signed informed consent form	X																	
Enrollment in the study		X																
CLINICAL EXAMINATION																		
Weight, height[4], PS (WHO)	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X
Digital rectal examination (clinical stage)	X	X[5]							X		X	X	X	X	X	X	X	X
Uroflowmetry		X																
Medical history of prostate cancer		X																
Grading of functional digestive, urinary and sexual symptoms (NCI-CTCAE V4.03)		X		X	X	X		X	X	X	X	X	X	X	X	X	X	X
QUESTIONNAIRES																		
QLQ-C30 and QLQ-PR25		X							X		X	X	X	X	X	X	X	X
IPSS		X						X	X		X	X	X	X	X	X	X	X
IIEF5		X						X	X		X	X	X	X	X	X	X	X
LABORATORY TESTS																		
CBC, platelets		X																
PT, PTT, and INR		X																
PSA		X						X		X	X	X	X	X	X	X	X	X
PATHOLOGICAL EVALUATION																		
Gleason score; number of positive biopsies, total number of biopsies; total length of cancer on biopsies; total length of biopsies	X																	
PARACLINICAL INVESTIGATION																		
Multi-parametric MRI (pelvic and prostate)	X[2]								X		X		X		X	X	X	X
Choline PET scan	X[3]																	
TNM evaluation	X																	
TRANSLATIONAL RESEARCH																		
Prostrate tumor biopsies (Initial before any treatment and at recurrence before SBRT)		X[6]																

1.Patient will be contacted by phone 14 weeks after starting SBRT to assess toxicity; an additional visit may be scheduled if required; 2 .Before inclusion, during regular follow-up and in case of biochemical recurrence after SBRT; 3 .Before inclusion and in case of biochemical recurrence after SBRT; 4.Patient's height will only be measured at the screening visit; 5. If not done at the screening visit.; 6.Only applicable for patients who have consented to participate in the biological ancillary study (see section 8.)

254x190mm (96 x 96 DPI)

GETUG-AFU 31: a phase I/II multi-center study evaluating the efficacy of repeat stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation therapy.

Appendix: statistical model, simulation study

Statistical considerations

A TITE-CRM method with an empiric dose-toxicity model in a Bayesian framework will be used for the dose-finding part of the trial to identify the recommended dose. The target dose-limiting toxicity (DLT) probability is set at p(DLT)=0.25. Three dose levels of SBRT are to be considered: 5 x 5 Gy (DL-1), 5 x 6 Gy (DL1), 6 x 6 Gy (DL2). The starting dose level is 5 x 6 Gy and dose level 5 x 5 Gy will be explored in case of DLT at the starting dose level. DLTs are evaluated during the 18 weeks following the initiation of salvage-SBRT. Observations of patients who have no DLT at the time of the analysis but have not completed the DLT assessment period will be down-weighted in the likelihood, proportionally to the length of follow up.

The Phase I part of the study will include 3 patients at the first dose level. Radiation dose levels for further patients will be defined based on the estimate of the probability of DLT at each dose-level considering all available information accumulated so far. Patients will be treated at the best current estimate of the recommended dose i.e. the dose associated with an estimated probability of DLT the closest to the target 0.25. Patients may eventually be treated at a dose below the dose recommended by the model for safety reasons. The patients can be recruited with no minimal time interval between successive inclusions. Two additional rules will be applied during dose escalation: no dose skipping and no escalation if at least 1 DLT is observed in the last 3 patients.
The dose-escalation part of the study will terminate once 10 patients have been treated and evaluated at a dose currently identified as the recommended dose. Further patients will then be accrued in the expansion cohort, where toxicity data collected over the first 18-week period and DLT assessment will be analyzed approximately every 10 patients with the possibility of modification of the recommended dose, based on model-based estimates.
The Phase II part of the study will need to include 44 patients, including the patients recruited in the dose-finding part of the phase I allocated at the dose level finally identified as the recommended dose. Thus, a minimal sample size of 47 patients will be required in this Phase I/II study (in the case of inclusion of 44 patients at dose level 2 + 3 patients at dose level 1).

Statistical model for dose escalation

A one-parameter empirical power model will be used to assess the relation between the dose level and the probability of DLT: $F(d,\alpha) = p_d^{\exp(\alpha)}$ where $F(d,\alpha)$ is the estimated probability of DLT at dose-level d, p_d is the prior probability of DLT at dose level d, and α is the unknown parameter to be estimated by the model. The vector $\{p_{0d}\}$ represent the initial guesses of toxicity probabilities, reflecting the clinicians' prior belief. The skeleton of initial guesses of toxicity probabilities $\{p_{0d}\}$ is numerically calibrated using the Lee and Cheung approach (ref ClinTrials 2009) and using the getprior function of R, ensuring good design's operating characteristics. After discussion with the clinicians, the delta defining the indifference interval was set at 0.05 (p(DLT)=0.25 +/- 0.05, i.e. indifference interval: 0.20 to 0.30) and the prior MTD (MTD_0) at the 2nd dose level, meaning that the clinicians believe, a priori, that the 2nd dose (6 x 6 Gy) is probably the MTD. This yields a vector of prior probabilities $\{p_{0k}\}$ equal to 0.08, 0.16 and 0.25 for dose level -1 (5 x 5Gy), dose level 1 (5 x 6 Gy) and dose level 2 (6 x 6 Gy). The clinicians confirmed that it was in accordance with their initial guesses. A non-informative prior distribution Normal (0, 1.34) has been assigned for α in the Bayesian

computation. The simulation study below confirmed that the operating characteristics and the behavior of the model defined with these parameters were reasonable.

Operating characteristics:

The operating characteristics of the proposed design were evaluated using the R titesim function written by Cheung, and considering six different scenarios:

- highly toxic,
- moderately toxic at dose levels -1 and 1, highly toxic at dose level 2
- moderately toxic et every dose level,
- similar with prior probabilities,
- close to the probabilities but a little less toxic,
- little toxic

For the simulation study, we considered that the trial would recruit 47 patients, which is the minimal sample size required in this Phase I/II study.
The following rules were implemented: no dose skipping in escalation, and no escalation if >1 DLT observed among < 3 patients.
For each case, 1000 trials were simulated. The Monte Carlo estimation of the percentage of dose selection, the average number of patients treated at each dose level, the average number of observed DLTs at each dose level demonstrated that the modified CRM design can efficiently identify the MTD, with a reasonable probability of overdosing, and expose few patients to toxicity.
A second set of simulations was performed considering a sample size of 13 patients, which is the minimal expected recruitment in the Phase I part of the study. As expected, the performance is much better when the reassessment is continued during the expansion phase (Phase II part). This is one of the advantages of the CRM method.

Figure 1: Scenarios studied

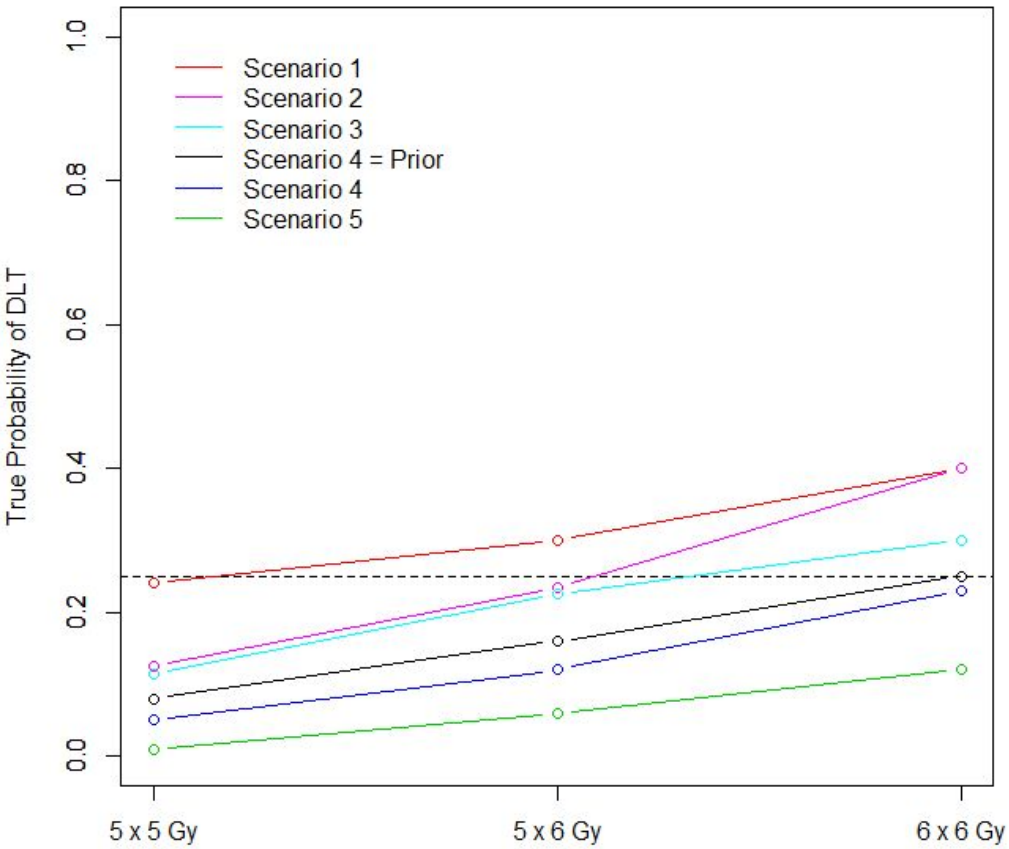

Table 1 : Operating characteristics for five different scenarios for the probability of DLT per dose

1a – Simulation for a recruitment of 47 patients (minimal sample size required in this Phase I/II study)

The grey row represents the true MTD (proba(DLT) closest to the target of 0.25.

SCENARIO 1 : highly toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.24	0.57	23.7	5.7	0.12
1 (5 x 6 Gy)	0.30	0.37	13.4	4.0	0.085
2 (6 x 6 Gy)	0.40	0.06	9.9	4.0	0.085

Expected number of DLTs over the whole trial (47 patients) = 13.7 / trial; 29% patients

SCENARIO 2: moderately toxic at dose levels -1 and 1, highly toxic at dose level 2

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.12	0.12	10.9	1.3	0.03
1 (5 x 6 Gy)	0.23	0.69	21.7	5.1	0.11
2 (6 x 6 Gy)	0.40	0.19	14.4	5.8	0.12

Expected number of DLTs over the whole trial (47 patients) = 12.1 / trial; 26% patients

SCENARIO 3: moderately toxic at every dose level

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.12	0.08	8.0	1.0	0.02
1 (5 x 6 Gy)	0.23	0.52	17.0	3.9	0.08
2 (6 x 6 Gy)	0.30	0.40	22.0	6.7	0.14

Expected number of DLTs over the whole trial (47 patients) = 11.6 / trial; 24% patients

SCENARIO 4 : true proba(DLT) = prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.08	0.006	3.2	0.3	0.01
1 (5 x 6 Gy)	0.16	0.22	11.3	1.8	0.04
2 (6 x 6 Gy)	0.25	0.78	32.5	8.2	0.17

Expected number of DLTs over the whole trial (47 patients) = 10.3 / trial; 22% patients

SCENARIO 5: little less toxic than prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.05	0.001	2.2	0.1	0.002
1 (5 x 6 Gy)	0.12	0.09	8.4	1.0	0.02
2 (6 x 6 Gy)	0.23	0.91	36.4	8.4	0.18

Expected number of DLTs over the whole trial (47 patients) = 9.5 / trial; 20% patients

SCENARIO 6: little toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.01	0	0.8	0.003	<0.001
1 (5 x 6 Gy)	0.06	0	2.3	0.1	0.002
2 (6 x 6 Gy)	0.12	1.0	43.9	5.3	0.113

Expected number of DLTs over the whole trial (47 patients) = 5.4 / trial; 11.5% patients

*% of DLT: mean n. of DLT / total number of patients

1b – Simulation for a recruitment of 13 patients (minimal sample size required in the Phase I part of the study)

The grey row represents the true MTD (proba(DLT) closest to the target of 0.25.

SCENARIO 1 : highly toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.24	0.52	4.7	1.1	0.08
1 (5 x 6 Gy)	0.30	0.27	2.7	0.8	0.06
2 (6 x 6 Gy)	0.40	0.21	5.6	2.2	0.17

Expected number of DLTs over the whole trial (13 patients) = 4.1 / trial; 31% patients

SCENARIO 2: moderately toxic at dose levels -1 and 1, highly toxic at dose level 2

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.12	0.30	3.8	0.5	0.04
1 (5 x 6 Gy)	0.23	0.39	3.2	0.7	0.05
2 (6 x 6 Gy)	0.40	0.31	6.0	2.4	0.19

Expected number of DLTs over the whole trial (13 patients) = 3.6 / trial; 28% patients

SCENARIO 3: moderately toxic at every dose level

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.12	0.21	3.0	0.4	0.03
1 (5 x 6 Gy)	0.23	0.33	3.0	0.7	0.05
2 (6 x 6 Gy)	0.30	0.46	7.0	2.1	0.17

Expected number of DLTs over the whole trial (13 patients) = 3.2 / trial; 25% patients

SCENARIO 4 : true proba(DLT) = prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.08	0.09	2.1	0.2	0.02
1 (5 x 6 Gy)	0.16	0.27	2.8	0.5	0.04
2 (6 x 6 Gy)	0.25	0.64	8.0	2.0	0.15

Expected number of DLTs over the whole trial (13 patients) = 2.7 / trial; 21% patients

SCENARIO 5: little less toxic than prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.05	0.05	1.6	0.1	0.01
1 (5 x 6 Gy)	0.12	0.21	2.7	0.3	0.02
2 (6 x 6 Gy)	0.23	0.74	8.7	2.0	0.15

Expected number of DLTs over the whole trial (13 patients) = 2.4 / trial; 18% patients

SCENARIO 6: little toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.01	0.004	0.6	0.01	0.001
1 (5 x 6 Gy)	0.06	0.04	1.8	0.09	0.007
2 (6 x 6 Gy)	0.12	0.96	10.6	1.3	0.10

Expected number of DLTs over the whole trial (13 patients) = 1.4 / trial; 11% patients

*% of DLT: mean n. of DLT / total number of patients

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym GETUG AFU 31 Phase I/II Multi-center Study Evaluating the Efficacy of Repeat Stereotactic Radiation in Patients With Intraprostatic Tumor Recurrence After External Radiation Therapy (STEREO-RE-PRO)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ClinicalTrials : NCT03438552
	2b	All items from the World Health Organization Trial Registration Data Set IdRCB : 2017-A00008-45
Protocol version	3	Date and version identifier version n°3.0 – 26/08/2016
Funding	4	Sources and types of financial material, and other support Support by a grant of National Institute of Cancer (INCA)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Docteur David PASQUIER Centre Oscar Lambret - Département de Radiothérapie 3, rue Fréderic Combemale - BP307 59020 Lille Cedex Tél : 03.20.29.59.11 - Fax : 03.20.29.58.96 E-mail : d-pasquier@o-lambret.fr
	5b	Name and contact information for the trial sponsor **UNICANCER** 101 Rue de Tolbiac, 75654 Paris Soazig NENAN +33 (0)185 343 113 s-nenan@unicancer.fr Meryem BRIHOUM +33 (0)1 80 50 12 95 m-brihoum@unicancer.fr

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities None
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention No standard treatment in this setting; to evaluate efficacy and safety of stereotactic body radiotherapy
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses **Primary objective** : Selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity observed during the 18 weeks following the initiation of salvage-SBRT. Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate **Secondary objectives** Evaluation of acute and late genitourinary toxicities of the salvage-SBRT Estimate the efficacy of the salvage-SBRT in terms of clinical progression-free survival and overall survival Evaluation of Quality of life after salvage-SBRT

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Study Type: Interventional ; phase I/II Primary Purpose: Treatment Intervention Model: Sequential Assignment Masking: Open Label Endpoint Classification: Safety/Efficacy Study Enrollment: 47

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Centers are hospitals and clinics (see below) : Centre François Baclesse, Caen, France Principal Investigator: Marlon SILVA Centre Jean Perrin, Clermont-Ferrand, France Principal Investigator: Geneviève LOOS Centre George François Leclerc, Dijon, France Principal Investigator: Gilles CREHANGE Centre Oscar Lambret, Lille, France Principal Investigator: David PASQUIER Centre Léon Bérard, Lyon, France Principal Investigator: Pascal Pommier Institut régional du Cancer de Montpellier, Montpellier, France Principal Investigator: David AZRIA Groupe Hospitalier Pitié-Salpétrière, Paris, France Principal Investigator: Philippe MAINGON ICO -Site René Gauducheau, Saint-Herblain, France Principal Investigator: Stephane SUPIOT Institut de Cancérologie Lucien Neuwirth, Saint-Priest-en-Jarez, France Principal Investigator: Nicolas MAGNE

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

Minimum Age: 18 Years
Gender: Male
Accepts Healthy Volunteers?: No

Inclusion Criteria:

1. Biochemical recurrence occurring at least 2 years after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL)
2. T1-T2c and PSA ≤20 ng/mL and Gleason score ≤7 at initial diagnosis of prostate cancer before the initial/first treatment.
3. Recurrence of prostatic adenocarcinoma proven by histology following radiotherapy by transrectal or transperineal sextant biopsies of the two lobes of the prostate, with a minimum of 12 biopsies, irrespective of Gleason score. Biopsies of the seminal vesicles are optional.
4. Clinical stage T1-T2 on relapse; unilateral extracapsular extension (T3a) on MRI permitted except posteriorly relative to the rectum
5. Estimated clinical target volume (CTV) / prostate volume < 0.5 based on imaging and biopsies
6. Pelvic and prostatic assessment by multiparametric MRI- Absence of pelvic or metastatic recurrence proven by choline PET scan
7. Performance status WHO 0-1
8. PSA level ≤10 ng/mL at baseline (before salvage-SBRT)
9. PSA doubling time >10 months
10. International Prostate Cancer Score (IPSS) ≤12
11. Uroflowmetry with a maximum flow rate >10 mL/s, a postvoid residual urine volume <150 mL, and a urine volume >150 mL.
12. No other anti-cancer treatment since the external radiotherapy administered as first-line treatment
13. No other anti-cancer treatment planned for the current recurrence
14. No contraindication to fiducial marker implants; haemostatic disorders must be corrected before implantation
15. Age >18 years
16. Life-expectancy greater than or equal to 5 years (Lee scale)
17. Patient registered with a health insurance system
18. Patient who has signed the informed consent form
19. Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests, and other study procedures indicated in the protocol.

Exclusion Criteria:

1. Lymph node or metastatic spread
2. Late post-radiotherapy urinary or gastrointestinal toxicity of grade ≥2 (following primary radiotherapy)
3. Other cancers in the last 5 years except for non-melanoma-type skin cancer
4. History of inflammatory bowel disease
5. Anticoagulant treatment
6. Contraindications to undergoing MRI
7. Prostate volume >80 cc
8. Transurethral resection of the prostate (TURP) in the 6 months before registrations
9. Presence of rectal telangiectasia grade 3 classified by the Vienne Rectoscopy Score (obligatory rectoscopy)
10. Previous rectal surgery
11. Patients unable to undergo medical follow-up in the study for geographical, social or psychological
12. Person deprived of their liberty or under protective custody or guardianship
13. Patients enrolled in another therapeutic study

All patients during the SBRT planning with a ratio of clinical target volume (CTV) / prostate volume > 0.5 will be withdrawn from the study. These patients will be considered as not evaluable and will not be treated within the context of the study.

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Focal salvage SBRT (5x6 Gy, 6x6 Gy, 5x5 Gy)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Anticoagulant treatment
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Primary Outcome Measure:** [Time Frame: 18 weeks] Selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity observed during the 18 weeks following the initiation of salvage-SBRT. The dose-escalation part of the study will terminate once 10 patients have been treated and evaluated at a dose currently identified as the recommended dose. [Time Frame: 6 years] Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate **Secondary Outcome Measure:** 1. Time Frame: 3 years] Evaluation of acute and late genitourinary toxicities of the salvage-SBRT 2. [Time Frame: 6 years] Estimate the efficacy of the salvage-SBRT in terms of clinical progression-free survival and overall survival 3. [Time Frame: 6 years] Evaluation of Quality of life after salvage-SBRT
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations 47 patients **Sample Size Calculations:** Required number of patients to be included: minimum 47 patients. The total sample size will depend upon the number of patients allocated at the different dose levels in the dose-finding parts of the trial. A total of 44 patients allocated at the recommended dose and evaluable at 3 years are required for the main analysis of the Phase II part of the trial to ensure an 85%-power if 3-year bRFS is p1=0.70, with a test against p0=0.50 at a one-sided 5%-alpha level.
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Communication and follow-up of the participating centers
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigne
Implementation	16c	Who will generate the allocation sequence: who will enrol participants: and who will assign participants to interventions:
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how Not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Not applicable

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Describe in protocol and data management procedures
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) Not applicable
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Not applicable

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Coordinator : validate the risk analysis (LIR) and the monitoring plan Project Manager : determine the risk analysis (LIR) and write the monitoring plan Clinical Research Associate (CRA) :perform monitoring according the monitoring plan
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct This point is provided by the vigilance unit of the sponsor. All details are described in the protocol
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Actually and according the risk analysis, no audit is planned

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval N° IdRCB : 2017-A00008-45 Initial Approval by CPP Nord-Ouest I (Committee for the Protection of Personnes/Ethic committee) : 25/07/2017 Approval Number: CPP3517-I
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) Each major protocol amendment is submitted to authorities for approval. After approval, it is communicated to all the actors of this project (investigators, trial centers, trial registry ….)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Principal Investigator or sub-investigator
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Collected by investigators and CRA on each trial centers. These data are anonymized. Shared on the eCRF. There is a control access on the eCRF
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site None
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Directly on the eCRF

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions A publication is planned; no publication restriction.
	31b	Authorship eligibility guidelines and any intended use of professional writers Coordinator will be the first author; co investigators will be authors.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code N/A
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

GETUG-AFU 31: a phase I/II multi-center study evaluating the safety and efficacy of salvage stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation therapy; study protocol

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Urology
Keywords:	prostate cancer, stereotactic body radiation therapy, recurrent prostate cancer, salvage radiotherapy

GETUG-AFU 31: a phase I/II multi-center study evaluating the safety and efficacy of salvage stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation therapy; study protocol

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ARTICLE SUMMARY

Introduction. Prostate cancer is the third most important cancer in terms of mortality in men. No standard local treatment exists for patients with an intraprostatic recurrence after radiotherapy. Stereotatic body radiotherapy (SBRT) could be a curative treatment for local recurrence.

Methods and Analysis. We plan to perform a multicenter prospective phase I/II study including at least 47 patients. Eligible patients are patients with biochemical recurrence occurring at least 2 years after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL):

- T1–T2c and PSA ≤20 ng/mL and Gleason score ≤7 at initial diagnosis before the initial/first treatment;
- Recurrence of prostatic adenocarcinoma proven by histology following radiotherapy by transrectal or transperineal sextant biopsies of the two lobes of the prostate, with a minimum of 12 biopsies, irrespective of Gleason score;
- Clinical stage T1-T2 on relapse;
- Pelvic and prostatic assessment by multiparametric MRI;
- Absence of pelvic or metastatic recurrence proven by choline or PSMA PET scan;
- PSA level ≤10 ng/mL at baseline (before salvage-SBRT), PSA doubling time >10 months, IPSS≤12.

The phase I primary objective is the selection of the recommended dose for salvage-SBRT (5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity. The dose of salvage-SBRT will be selected using a Time-to-Event Continual-Reassessment-Method based on dose-limiting toxicity defined as grade ≥3 gastrointestinal or urinary toxicity or any other grade 4 adverse event. The phase II primary objective

is to estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate. Phase II secondary objectives are: acute and late toxicities, quality of life, clinical progression free survival and overall survival.

Ethics and Dissemination. The study has received ethical approval from the Ethics committee "Ile-de-France III". Academic dissemination will occur through publication and conference presentations.

Trial registration: NCT03438552

Date of trial registration: November 14, 2017

Strengths and limitations of this study funding

- Very innovative trial evaluating stereotactic body radiotherapy for recurrent prostate cancer, the only ongoing trial of this kind to our knowledge
- Clinical trial supported by the GETUG-AFU cooperative group, expert in the field, and funded by the French National Cancer Institute (INCa)
- Time-to-Event Continual Reassessment Method, a more appropriate method than the 3+3 design to quantify late toxicity in phase I radiotherapy trials
- Proof-of-concept study; therefore, further research will be required

Keywords: prostate cancer, stereotactic body radiation therapy, recurrent prostate cancer

Background

Prostate cancer is the third most important cancer in terms of mortality in men (after lung and colorectal cancer), and the fourth leading cancer overall [1]. In the European Union, it was predicted that 72600 patients would die from prostate cancer in 2015. The rate of recurrence/relapse of prostate cancer after primary external beam radiotherapy varies from 21% to 65% depending on the study [2,3]. Zelefsky et al. performed biopsies on 339 patients after treatment with 3-dimensional conformal radiotherapy (3D-CRT) or intensity modulated RT for T1c-T3 stage prostate cancer, with a minimum follow-up of 2.5 years [2]. They found that the rate of positive biopsy according to radiation dose was 65% for <70.2 Gy, 38% for 70.2 Gy, 27% for 75.6 Gy, and 25% for ≥81 Gy. A two years biopsy was performed in 312/843 patients included in MRC RT01 trial. A positive biopsy was prognostic of worse biological progression free survival compared with negative and suspicious biopsies, hazard ratio (HR)=4.81 (95% confidence interval [CI]: 2.50-9.26, p<0.001). The estimate for survival was HR=1.58 (95% CI: 0.52-4.78, p=0.42).

In the literature and guidelines a minimum time of two years is recommended between radiotherapy and prostate biopsies to minimize the risk of false positive and this two-year interval has been selected in our study. This risk decreases over time. Nevertheless the guidelines recommend to perform prostate biopsies before any salvage treatment, and the diagnosis is based on imaging too in our study.

D'Amico reported that the 5-year prostate cancer mortality rate after biochemical recurrence in patients who received external beam radiotherapy for localized prostate cancer depended on the pretreatment Gleason score: 24% for ≤6 score, 40% for 3+4 score, and 59% for 4+3 or higher score (p=0.01); as well as, on the pretreatment PSA level: 22% for ≤10 ng/mL, 40% for >10 and ≤20 ng/mL, and 60% for >20 ng/mL (p=0.04) [4]. In addition, Buyyounouski reported that the interval to biochemical recurrence was an important factor in identifying men at high risk of distant metastasis and death [5]. An interval to biochemical recurrence (PSA nadir + 2 ng/mL) of <18 vs. ≥18 months was associated with a 5-year distant metastasis rate of 52% vs. 20% (p<0.0001), and a prostate-cancer

specific mortality rate of 36% vs. 6% (p=0.0001). Thus late relapse and long PSA doubling time are prognostic factors of solely intraprostatic relapse.

Prostate-specific antigen (PSA) is a validated biomarker for prostate cancer. PSA levels are extensively used to monitor response to radical prostatectomy (RP) and external-beam radiotherapy (EBRT). The serum PSA level is an important surrogate for recurrence in prostate cancer patients. The recommendations of the Radiation Therapy Oncology Group (RTOG) ASTRO Phoenix Consensus Conference suggested that an increase of ≥2 ng/mL from the nadir be used to define recurrence/relapse [6]. It is important to note that biochemical recurrence may indicate local or systemic disease recurrence, and may require prostate biopsy for confirmation particularly when local salvage treatments are being considered [7].

A number of different salvage treatments have been used after failure of primary radiotherapy. RP is more invasive than brachytherapy, ultrasound, high-intensity focused ultrasound (HIFU), and SBRT. Below is a brief discussion of the results obtained with each techniques and its associated toxicity and complications.

Salvage RP (SRP) is a treatment option after local recurrence following EBRT. However, the morbidity, including incontinence and erectile dysfunction, is higher than that observed with first-line RP patients. A systematic literature review [7] reported that the probability of biochemical relapse–free survival (bRFS) following SRP in prostate cancer patients was 47-82% after 5 years and 28-53% after 10 years. SRP has an increased risk of adverse events due to fibrosis and poor wound healing after radiotherapy. Furthermore, SRP after radiotherapy compared to primary RP has a significantly higher rate of urinary and gastrointestinal morbidity [8]. The review above [7], reported that the most frequent complications were anastomotic stricture (7-41%) and rectal injury (0-28%). The majority (50-91%) of men had erectile dysfunction before SRP and 80-100% after surgery. Post-operative urinary continence ranged from 21-90%.

In a recent review, salvage brachytherapy after EBRT is reported to achieve biochemical control rates of 20% to 89% (median follow-up: 19 to 108 months) [9]. Rates of genitourinary toxicities range

from 12% to 87% for grade 1-2, and 3% to 47% for grade 3-4 toxicities. Similarly, the rates of gastrointestinal toxicities range from 4% to 65% for grade 1-2, and 0% to 20% for grade 3-4 toxicities. Erectile dysfunction was observed in 2% to 95% of men. A phase II study of salvage high-dose-rate brachytherapy (HDR) for treating recurrent prostate cancer after definitive external beam radiotherapy was reported by Yamada [10]. The 42 patients enrolled, with biopsy proven recurrence, were treated with salvage HDR (iridium-192) with a resulting bRFS at 5 years of 68.5% (median follow-up of 36 months [range: 2-66 months]). Acute genitourinary toxicity was observed: grade 1, 38% of patients and grade 2: 40%. Similarly, late genitourinary toxicity was observed: grade 1, 38% of patients and grade 2, 48%. In addition, 1 patient had a grade 3 urinary incontinence and 3 had grade 3 urethral strictures. Late gastrointestinal toxicities were observed: grade 1, 43% of patients and grade 2, 14%. More recently, a study of 83 prostate cancer patients with local recurrence after radiotherapy treated with high-dose-rate brachytherapy was reported [11]. The 3-year and 5-year bRFS were 76% and 67%. A phase II study of the RTOG in 100 patients was recently presented: twelve (14%) experienced late grade 3 genitourinary/gastrointestinal adverse effects. This rate of late grade 3 toxicity (14%) was not unacceptable by the predetermined protocol specification, without any grade 4-5 events. The only factor predictive of late toxicity was implant dose, underlining the need for meticulous planning and technique to limit the final delivered dose [12]. In France, a phase II study, “Brachytherapy for Recurrent Prostate Cancer” (CAPRICUR) was recently completed [13].

HIFU is another less invasive salvage treatments following recurrence. HIFU uses focused ultrasound to generate heat (85°C) which induces tissue necrosis [14]. The following studies have investigated the use of salvage-HIFU after initial radiotherapy. A French group treated 290 men with biopsy-confirmed recurrent prostate cancer, after radiotherapy, with salvage HIFU [15]. At 7 years, the cancer-specific survival rate was 80% and the metastasis-free survival rate was 79.6%. Recto-urethral fistula occurred in 0.4% of patients and 19.5% had grade 2/3 incontinence. Half of the patients also received hormone therapy. Survival without relapse at 5 years after HIFU, by D’Amico risk groups prior to their initial treatment, was 45% (favorable), 31% (intermediate risk) and 21%

(high risk). In this cohort, the grade ≤3 urinary incontinence levels were 23% (favorable), 14% (intermediate risk) and 9% (high risk). Nearly 8% of patients required an artificial sphincter following HIFU. Importantly, pubic osteitis occurred in 2.5% of patients despite adherence to parameters specific to HIFU following radiotherapy [15].

Cryotherapy is thermo-ablative treatment; the third–generation argon/helium-based cryotherapy system creates precise isotherms through ultrathin needles [16]. In a retrospective multicenter series pooling 279 patients, survival without biochemical relapse at 5 years was 54%. Prostatic biopsies showed tumor persistence in 32% of patients following cryotherapy [17]. In a paired case-controlled study, prostatectomy and cryotherapy were compared following radiotherapy. Survival without relapse (PSA nadir + 0.4 ng/mL) at 5 years was significantly lower after cryotherapy (21% vs. 61%, p<0.001); this was confirmed by the 5-year OS rate of 85%, cryotherapy, vs 95%, radical prostatectomy (p=0.001) [18]. Intermediate results from a study investigating third-generation cryotherapy as a salvage treatment of locally recurrent prostate cancer after radiotherapy was published [19]. The 5-year bRFS rate (Phoenix definition) was 43.5% and with a 5-year OS rate of 92.3%. Mild complications (grades 1 and 2) were reported including: mild incontinence (9.4%), acute rectal pain (31.3%), lower urinary tract symptoms (15.6%) and erectile dysfunction (57.1%). Grade 3 toxicities: incontinence (3.1%) and urethral sloughing (3.1%) were observed.

Androgen-deprivation therapy (ADT) alone (continuous or intermittent) is commonly given to patients with biochemical relapse after radiotherapy [20]. In a series based on data from a North American national registry (CaPSURE), 71% of patients were treated for biochemical relapse after prostatectomy or radiotherapy. ADT was initiated in 93% of these patients, and the remaining patients were treated with surgery, brachytherapy, cryotherapy, or repeat external radiotherapy [21]. ADT may cause adverse effects impacting patient's quality of life (including: hot flushes, erectile dysfunction and reduced libido, cognitive impairment, and anemia). The metabolic changes associated with hormone therapy may also increase the risk of cardiovascular morbidity. The reduction in bone mass is maximal in the first year and increases with the duration of castration; the

risk of fracture is increased in patients surviving for more than 5 years [22-23]. The guidelines suggest that a simple follow-up can be implemented for local recurrence in patients with a limited life expectancy or for those who do not wish to undergo local salvage treatment. The last European Association of Urology guidelines [24] recommended to perform salvage surgery in experienced centres due to the increased rate of side effects. It is recommended to offer/discuss HIFU, cryosurgical ablation and salvage brachytherapy to/with patients without evidence of metastasis and with histologically proven local recurrence and to inform patients about the experimental nature of these approaches. The level of evidence for each of these recommendations is 3 [24].

SBRT delivers highly conformal, high-dose radiation in a few fractions (hypofractionation), typically 5 to 7 fractions for prostate cancer. It is reported that tissues with a low α/β ratio, as for prostate cancer, are more sensitive to large doses of radiation per fraction. The surrounding normal tissue could have similar or higher α/β ratio. This suggests that hypofractionation (large radiation dose per fraction) may result in improved tumor control with limited toxicity. A pooled analysis of 1100 patients included in separate prospective phase II studies in 8 institutions was performed to evaluate the effectiveness of SBRT as a first-line treatment for localized prostate cancer [25]. The SBRT was delivered by CyberKnife with a median dose of 36.25 Gy in 4-5 fractions. The 5-year bRFS rate was 93% for all patients. Thus relapse-free survival rates after SBRT compare favourably with other definitive treatments for low and intermediate-risk patients with a short follow up. SBRT is well tolerated with a low effect on quality of life [25-28]. In addition sexual function appeared to be spared in the majority of patients [25-28].

SBRT has also been used as a salvage treatment following failure of external radiotherapy. Jereczek-Fossa et al. published data on 34 consecutive patients treated with robotic SBRT for isolated recurrent primary, lymph node, or metastatic prostate cancer [29]. Of the 34 patients, 15 patients had intraprostatic recurrence, confirmed by biopsy, and were treated with SBRT (CyberKnife) with a median dose of 30 Gy in 5 fractions. Fourteen patients showed a biochemical response; the median survival without recurrence was 13 months. Five patients presented a clinical relapse, including one

new intraprostatic recurrence. Urinary toxicity was low, with a grade 3 urinary toxicity in only one patient. No case of acute or late gastrointestinal toxicity was reported. This good gastrointestinal tolerability has subsequently been confirmed [29-32]. In Fuller et al twenty-nine patients were treated in a phase II trial with stereotactic radiotherapy for intraprostatic recurrence [30]. Eligible patients had to present biopsy-proven intraprostatic recurrence graded T1 to T3N0M0 more than 2 years post-radiotherapy and without a pre-existing grade >1 radiotherapy toxicity. The prior median dose delivered was 73.8 Gy and the median interval between the treatments was 88 months. The dose delivered to the entire gland was 34 Gy in five fractions over 5 days (heterogeneous intraprostatic dose of up to 50 Gy). With a median follow-up of 24 months, survival without recurrence was 82%. Toxicity was acceptable, with 18% grade ≥2 urinary toxicity, including one patient with a grade 4 toxicity, and no late gastrointestinal toxicity above grade 1. Particular attention should be given to patients who still exhibit urinary toxicity after initial radiotherapy [30]. Our preliminary retrospective results in 23 patients treated for this indication were published recently [31]. A total dose of 36 Gy was prescribed in 6 fractions of 6 Gy. Nineteen patients had a whole-gland and four a partial treatment. Median follow-up was 23 months (range 6 to 40 months). We observed no grade 4 or 5 toxicity. Two patients presented grade 3 toxicities. Others toxicities include urinary (5 grade 2 and 9 grade 1) and rectal toxicities (2 grade 2 and 2 grade 1). The dose levels selected in our study are close to those used in de novo patients, and the same as those described in retrospective salvage treatment series. These schemes seem to provide an acceptable compromise between efficacy and toxicity but have not been evaluated prospectively.

To date, no standard local treatment exists for patients with an intraprostatic recurrence after radiotherapy [33]. A number of treatments options exist including: radical prostatectomy, brachytherapy, HIFU, cryotherapy, and stereotactic radiotherapy. The literature to date consists mainly of retrospective and small prospective series making it difficult to assess and compare these techniques. In recent years, SBRT has been used to treat localized prostate cancer in the primary setting but also as a salvage treatment after failure of radiotherapy. The initial results of these

retrospective studies are promising, with respect to survival and tolerance, but further studies are required to confirm these initial results. Our proposed study will provide further evidence of SBRT as a supplementary non-invasive curative treatment for local recurrence following radiotherapy. This study could provide the foundation for prospective studies comparing the available salvage treatments after radiotherapy.

Methods/design

This study is approved by the Ethics committee "Ile de France III" (2017-A00008-45) and is registered on clinicaltrials.gov (NCT03438552). This multicenter open-labelled phase I/II study will initially select the SBRT scheme (phase I), either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy. The effectiveness of SBRT scheme selected in phase I will then be evaluated in a single-arm multicenter phase II study.

PHASE I primary objective and assessment:

Selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity observed during the 18 weeks following the initiation of salvage-SBRT. The dose of salvage-SBRT will be selected using a Time-to-Event Continual Reassessment Method [34-36] based on dose-limiting toxicity defined as grade ≥3 gastrointestinal or urinary toxicity or any other grade 4 adverse event observed during the 18 weeks following the initiation of salvage-SBRT.

PHASE II primary objective and assessment:

Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate (Phoenix definition: increase in serum total PSA ≥2 ng/mL above the nadir). Time to biochemical relapse-free survival will be computed from registration. Patients alive without biochemical progression at the time of the analysis will be censored at the last follow-up date. In the event of death, whatever the cause of death, the patient will be considered as a failure.

PHASE II secondary objective(s) and assessment:

- Acute and late genitourinary and gastrointestinal toxicities over the first 3 years according to the NCI-CTCAE V4.03 classification (June 14th, 2010), International prostate Symptom Score (IPSS) score for urinary symptoms, and International Index of Erectile Function (IIEF5) for erectile function. Patients will be followed for 5 years after salvage SBRT to assess late toxicity. Patients with second biochemical recurrence will not be excluded in order to assess late toxicity.
- Quality of life will be evaluated based on the EORTC QLQ-C30 and QLQ-PR25 scales. The Time Until Definitive Deterioration (TUDD) will be computed from registration until the first observation of a definitive deterioration of the quality of life, defined as a score decreased by 10 points (in the case of global health scale and functional scales) or increased by 10 points (in the case of symptom scales) compared to the score at baseline, without later improvement superior to 10 points compared to baseline score.
- Clinical progression-free survival is defined as the time interval between the date of registration and the date of clinical progression (local progression assessed by the physical examination, or appearance of metastatic lesions) or death irrespective of the cause.
- Overall survival is defined as the time interval between the date of registration and the date of death irrespective of the cause.
- Erythroblast transformation-specific related gene (ERG) fusion expression will be evaluated using immunohistochemistry (IHC) tests. ERG fusion and androgen-receptor splice variant 7 (ARV7) expression will be evaluated on biopsies before the first radiotherapy treatment (at diagnosis, if available) and before salvage radiotherapy after biochemical recurrence.

DIAGNOSIS AND INCLUSION CRITERIA:

- Biochemical recurrence occurring at least 2 years after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL)

- T1–T2c and PSA ≤20 ng/mL and Gleason score ≤7 at initial diagnosis of prostate cancer before the initial/first treatment.
- Recurrence of prostatic adenocarcinoma proven by histology following radiotherapy by transrectal or transperineal sextant biopsies of the two lobes of the prostate, with a minimum of 12 biopsies, irrespective of Gleason score. Biopsies of the seminal vesicles are optional.
- Clinical stage T1-T2 on relapse; unilateral extracapsular extension (T3a) on magnetic resonance imaging (MRI) permitted except posteriorly relative to the rectum
- Estimated clinical target volume (CTV) / prostate volume < 0.5 based on imaging and biopsies
- Pelvic and prostatic assessment by multiparametric (mp) MRI
- Absence of pelvic or metastatic recurrence proven by choline positron emission tomography (PET) scan
- Performance status WHO 0-1
- PSA level ≤10 ng/mL at baseline (before salvage-SBRT)
- PSA doubling time >10 months
- IPSS ≤12
- Uroflowmetry with a maximum flow rate >10 mL/s, a postvoid residual urine volume <150 mL, and a urine volume >150 mL.
- No other anti-cancer treatment since the external radiotherapy administered as first-line treatment
- No other anti-cancer treatment planned for the current recurrence
- No contraindication to fiducial marker implants; haemostatic disorders must be corrected before implantation
- Age >18 years

- Life-expectancy greater than or equal to 5 years (Lee scale)
- Patient registered with a health insurance system
- Patient who has signed the informed consent form
- Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests, and other study procedures indicated in the protocol.

EXCLUSION CRITERIA:

- Lymph node or metastatic spread
- Late post-radiotherapy urinary or gastrointestinal toxicity of grade ≥2 (following primary radiotherapy)
- Other cancers in the last 5 years except for non-melanoma-type skin cancer
- History of inflammatory bowel disease
- Anticoagulant treatment
- Contraindications to undergoing MRI
- Prostate volume > 80 cc
- Transurethral resection of the prostate (TURP) in the 6 months before registration
- Presence of rectal telangiectasia grade 3 classified by the Vienne Rectoscopy Score (obligatory rectoscopy) [37,38]
- Previous rectal surgery
- Patients unable to undergo medical follow-up in the study for geographical, social or psychological
- Person deprived of their liberty or under protective

INTERVENTION

A flow chart presenting the different steps from inclusion until treatment is presented in Fig. 1. Five or six fractions, at a level of 5 or 6 Gy per session (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy), will be delivered over a maximum of 12 days to provide a total dose of 25 to 36 Gy. This radiotherapy may

be administered with the CyberKnife® or a linear accelerator allowing stereotactic radiotherapy. The patient will be placed in a stable and reproducible supine position. Intraprostatic markers (fiducials) will be implanted before the dosimetric CT-scan and MRI are performed. The choice of markers is left to the discretion of each participating site (gold seeds, etc.). The site needs to ensure that the repositioning of the prostate is precise (≤2 mm), allowing an exact overlay between dosimetric MRI and computed tomography (CT)-scan. The implant of fiducials is obligatory irrespective of the stereotactic radiotherapy technique used. The fiducials can be implanted during or after the biopsies. The CT-scans and MRIs registration is guided by the fiducials. Each team can choose the fiducials visible on the MRI they wish to use and/or integrate a specific sequence during the centering MRI for better visualization.

An mpMRI and CT-scan will be carried out at least one week after fiducial implantation. CT-scan images should be acquired with the patient in the treatment position using the chosen immobilizing system, if required according to centers' standard procedures. An intravenous injection of a contrast product should be administered unless contraindicated. Acquisition should allow anatomical structures and markers (already implanted in the prostate) to be visualized. The bladder will be half-filled (neither full nor empty, i.e. a final voiding 90 minutes before the CT-scan followed by ingestion of 250-350 mL of water). The rectum will be empty and not distended. If necessary rectal enema can be used before CT-scan acquisition. Contiguous CT-scan slices ≤2 mm thick will be taken between the L5-S1 joint space and the small trochanters. After image transfer to a planimetric console, fiducial-based registration with the prostatic mpMRI will take place in order to provide a better definition of the Gross Target Volume (GTV) and prostatic contours, especially the apex. Fiducial-based CT-MRI registration is mandatory. Multimodality image registration with Choline PET is possible but not mandatory.

Delineation of the target volume will be carried out by a radiotherapist experienced in the definition of prostate volumes on CT-scans and MRIs. The mpMRI-defined contour will be integrated with the CT-scan derived contours in order to define tumor and the prostatic apex more precisely.

GTV will be represented by lesion defined on the multiparametric MRI +/- choline PET; a 5-7 mm margin around the GTV will be used to define the Clinical Target Volume (CTV). CTV is contained in the prostate, except in the case of extracapsular extension (unilateral extracapsular extension on MRI permitted except posteriorly relative to the rectum). In the case where the positive biopsy(ies) are outside and adjacent to the visible lesions on the MRI, the zone containing these biopsies must be included in the CTV so that the prostate cancer recurrence not visible on the MRI is included in the CTV. If no lesion is visible on the MRI and/or choline PET, the zone containing positive biopsies must be included in the CTV. For example: MRI +/-choline PET lesion in 3p and 4p according to ESUR guidelines, with positive biopsies in 1p, 3p and 4p: CTV = MRI GTV + 5 mm + the posterior right base. The total CTV should not be more than half of the total volume of the prostate by MRI. The planning target volume (PTV) will be obtained by an expansion of 2 mm around the CTV in this repeat radiotherapy context. This margin involves that the probability of coverage at 25, 30, or 36 Gy is low, so the reporting will include D2%, 50%, D98% and D95% to describe as much as possible delivered dose. Organs at risk constraints are specified in Table 1. Daily image guided radiation therapy is mandatory, intra fraction tracking is recommended.

Rectum	Bladder	Urethra + 3 mm
V27 Gy <2 cc	V27 Gy <5 cc	V24 Gy <30%
V12 Gy <20%	V12 Gy <15%	D_{max} (35 mm^3) <39 Gy
		V36 Gy <1 cc

Table 1. Organs at risk constraints

Quality control is particularly important in this setting of repeat radiotherapy. Before starting patient enrolments a “dummy-run” will be conducted: an anonymous clinical chart will be forwarded to all participating sites with clinical, scintigraphy (choline PET-scan), CT-scan and MRI data prior to repositioning. After delineating the relevant volumes, each site will have to perform a dosimetry

which will be centralized in order to verify that the constraints are being observed. For each site, the dosimetric data will be subject to a centralized review prior to SBRT administration in order to verify that constraints are being observed. Follow-up visits are described in Figures 1 and 2.

SAMPLE SIZE CALCULATION

Required number of patients to be included: minimum 47 patients. The total sample size will depend upon the number of patients allocated at the different dose levels in the dose-finding parts of the trial. A minimum of 13 patients will be recruited before the expansion phase is open (Phase II part). A total of 44 patients allocated at the recommended dose (recruited in the dose-escalation stage or in the expansion phase) and evaluable at 3 years are required for the main analysis of the Phase II part of the trial to ensure an 85%-power if 3-year bRFS is p1=0.70, with a test against p0=0.50 at a one-sided 5%-alpha level.

STATISTICAL CONSIDERATIONS

PHASE I

Three dose levels of SBRT are to be considered: 5 x 6 Gy, 6 x 6 Gy, and 5 x 5 Gy. The starting dose level is 5 x 6 Gy. The lower dose level, 5 x 5 Gy, will be considered if excessive toxicity is reported at the first dose-level (5 x 6 Gy). A TImeTo Event-Continuous Reassessment Method (TITE-CRM) with an empiric dose-toxicity model in a Bayesian framework will be used for the dose-finding part of the trial to identify the recommended dose. The target dose limiting toxicity (DLT) probability is set at p(DLT)=0.25. Observations of patients who have no DLT at the time of the analysis but have not completed the DLT assessment period will be down-weighted in the likelihood, proportionally to the length of follow up; for instance, if the last patient has been recruited 8 weeks before a new patient is available for enrolment, and is evaluated at week 10 with no DLT, then his observation is attributed a weight of 10/18=0.56.

At least three patients will be enrolled at the first dose-level and fully evaluated over the 18-week study period before the dose is escalated to the next dose-level. Radiation dose levels for further patients will be defined based on the estimate of the probability of DLT at each dose-level considering all available information accumulated so far. Patients will be treated at the best current estimate of the recommended dose i.e. the dose associated with an estimated probability of DLT the closest to the target 0.25. Patients may eventually be treated at a dose below the dose recommended by the model for safety reasons. The patients can be recruited with no minimal time interval between successive inclusions. During the dose-escalation part of the trial, safety data will have to be reported in the data base in real time. A monthly teleconference meeting with the participation of the biostatistician, the trial coordinator and a representative of the sponsor, to summarize toxicity observations and define the dose to be allocated to the next patient(s) will be held. Safety data will be discussed with an Independent Data Monitoring Committee (IDMC) at the end of the dose-escalation part of trial, or before if needed.

The dose-escalation part of the study will terminate once 10 patients have been treated and evaluated at a dose currently identified as the recommended dose. Further patients will then be accrued in the expansion cohort, where toxicity data collected over the first 18-week period and DLT assessment will be analyzed approximately every 10 patients with the possibility of modification of the recommended dose, based on model-based estimates.

Specifications of the model are detailed in appendix, as well as the results of a simulation study evaluating the operating characteristics of the proposed design.

PHASE II

The phase II is based on a one-stage design based on an efficacy endpoint (3-year bRFS). Assuming that information will be available for all patients at 3 years, the endpoint follows a binomial distribution. The design was thus defined considering exact tests, as published by A'Hern [39].

From the literature, the expected bRFS rate at 3 years is approximately 50% in this patient population with various salvage therapies. A 3-year bRFS equal to or lower than 0.50 is deemed insufficient for further evaluation of this approach [p0=0.50]. The considered alternative hypothesis is p1=0.70].

The Phase II part of the study will need to include 44 patients (including the patients recruited in the dose-finding part of the phase I, allocated at the dose level finally identified as the recommended dose). If all 44 patients are evaluable at 3 years, the treatment strategy will be considered to be insufficiently effective if ≤ 27 patients are alive without a biochemical relapse at 3 years.

The operating characteristics of the design are:

- p0=0.50, p1=0.70
- Defined Type I error = 0.05 (computed type-I error of the design = 0.048)
- Defined Power = 0.85 (computed power = 0.861)

If some patient data are censored before 3 years, the 3-year bRFS will be estimated using Kaplan-Meier method and the lower boundary of the 90% confidence interval will be compared to p0=0.50. The conclusion will be positive if we can reject the null hypothesis p0=0.50 at a one-sided 5% alpha level.

PATIENT AND PUBLIC INVOLVEMENT

Patients were not involved in the idea conception of this trial.

Patients were not involved in the design of this study nor in recruitment of the study.

Discussion

To date, no standard local treatment exists for patients with an intraprostatic recurrence after radiotherapy. A number of treatments options exist including: radical prostatectomy, brachytherapy, HIFU, cryotherapy, and more recently SBRT. These treatments are associated with a variety of genitourinary and gastrointestinal toxicities and complications. The literature to date consists mainly

of retrospective and small prospective series making it difficult to assess and compare these techniques. Philippou et al compared oncologic and toxicity outcomes of SRP versus nonsurgical therapies except SBRT with a meta-regression analysis. Oncologic and toxicity outcomes appear to be similar; however, all nonsurgical salvage modalities may be associated with better continence outcomes [40].

The sensitivity of PSMA-PET is higher than that of choline-PET for the detection of lymph node disease [41]. Unfortunately PSMA PET is not routinely available in France. A modification of the inclusion criteria is being drafted to allow PSMA PET if this examination becomes available during the study period. To have a high sensitivity, a lymph node staging must be extensive, which can have side effects in this context. Furthermore clinical and biological selection criteria (no high risk cancer before first treatment, PSA level, PSA doubling time,...) are designed to select the patients to have most likely intra-prostatic recurrence only.

The phase I part of GETUG-AFU 31 trial will evaluate SBRT dose of 30 Gy in 5 fractions, over 12 days, and then depending on tolerance, 36 Gy in 6 fractions over 12 days. The latter, 36 Gy in 6 fractions, is the current scheme used at the Oscar Lambret Centre for all repeat SBRT. This dose is higher than that described by Jereczek-Fossa et al. (30 Gy in 5 fractions) [29], discussed as being too low [30], but lower than the dose used by Fuller (38 Gy in 4 fractions) [30]. A lower dose (5 x 5 Gy) was used in Zerini et al [32]. We have decided to initially use a phase I study, using dose-limiting toxicity criteria, to establish the best dose (either 5 x 6 Gy, 6 x 6 Gy, or 5 X 5 Gy) for the phase II part of the study. In phase I radiotherapy trials, late complications are often not taken into account and there is currently no consensus on the methodology used for these studies. Although most phase I radiotherapy studies use a 3+3 design, it is not suitable for these studies as it does not assess late toxicity. More complex designs such as the TITE-CRM are recommended, which will shorten the duration of the entire trial and efficiently uses patient information throughout the study [42].

Abbreviations

GETUG-AFU: “Groupe d’Etude des Tumeurs Uro Genitales- Association Française d’Urologie”; PSA: prostate-specific antigen; RP: radical prostatectomy; EBRT: external-beam radiotherapy; SBRT: stereotactic body radiation therapy; HIFU: high-intensity focused ultrasound; bRFS: biochemical relapse–free survival; HDR: high dose rate; RTOG: radiation therapy oncology group; ADT: androgen-deprivation therapy; CTCAE: common toxicity criteria adverse events; Gy: Gray; TITE-CRM: Time-to-Event Continual Reassessment Method; IIEF: International Index of Erectile Function; CTV: clinical target volume; PTV: planning target volume; QOL: Quality of life; RTOG: Radiation Therapy Oncology Group; TUDD: time until definitive deterioration; ERG: Erythroblast transformation-specific related gene; IHC: immunohistochemistry; ARV7: Androgen-receptor splice variant 7; MRI: magnetic resonance imaging; TURP: transurethral resection of the prostate; CT: computed tomography; mpMRI: multiparametric MRI; PET: positron emission tomography; WHO: world health organization; GTV: gross tumor volume; DLT: dose limiting toxicity

Declarations

Ethics approval and consent to participate

The study has been submitted and approved by ethics committee (the ethical committee “Ile de France III” (2017-A00008-45) for all study sites. The study opened in February 2018.
A written informed consent will be obtained from the study participants.
There is an agreement between each participating center and Unicancer. Each protocol version is signed by the principal investigator. We have a copy of each signed document.
In France, according to the current law, a protocol can be subjected to any regional Ethics Committee, even if no hospital of this region takes part to the trial. The choice is made according to the workload of every committee. The opinion of this Ethics Committee applies to all the national centers.

Consent for publication

A signed informed consent is obtained from all patients included in the trial.

Availability of data and material

The data set used and/or analysed during the current study are available from the corresponding author on reasonable request. Not all data are obtained yet since the study is still ongoing.

Competing interests

None declared.

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Author contributions

Study Conception: DP. Revision of study design and protocol: DP, MCLD, ET, LC, MD, SN, ERL. Study coordination: DP, MCLD, ET, SN. All authors read and approved the final manuscript.

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None

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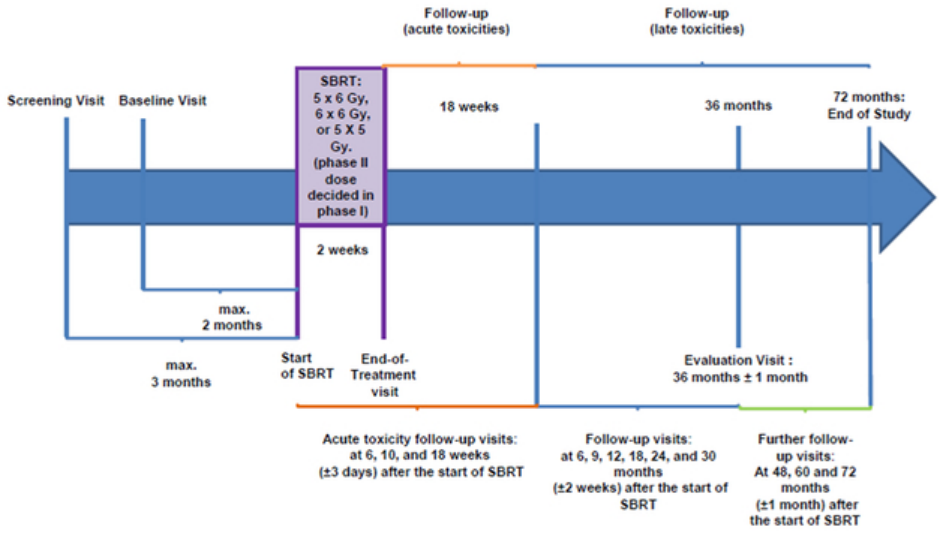
Figures legends

Fig. 1 Overview of study flow chart. SBRT: stereotactic body radiotherapy

Fig 2. Detailed description of study flow chart.

(1.Patient will be contacted by phone 14 weeks after starting SBRT to assess toxicity; an additional visit may be scheduled if required; 2 .Before inclusion, during regular follow-up and in case of biochemical recurrence after SBRT; 3 .Before inclusion and in case of biochemical recurrence after SBRT; 4.Patient's height will only be measured at the screening visit; 5. If not done at the screening visit.; 6.Only applicable for patients who have consented to participate in the biological ancillary study)



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	Screening	Baseline		End of RT visit (at last RT session)	Acute toxicity follow-up visits 6, 10, and 18 weeks (±3 days) after starting SBRT				Follow-up visits 6, 9, 12, 18, 24, and 30 (±2 weeks) after starting SBRT						Evaluation visit 36 months (±1 month) after starting SBRT	Further follow-up visits 48, 60 and 72 months (±1 month) after starting SBRT/End of Study		
Visits	**ScV**	**BV**		**End RT**	**W6**	**W10**	**W14[1]**	**W18**	**M6**	**M9**	**M12**	**M18**	**M24**	**M30**	**M36**	**M48**	**M60**	**M72/End of Study**
Eligibility criteria	X	X	Fiducial placement and treatment planning followed by SALVAGE-SBRT															
Signed informed consent form	X																	
Enrollment in the study		X																
CLINICAL EXAMINATION																		
Weight, height[4], PS (WHO)	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X
Digital rectal examination (clinical stage)	X	X[5]							X		X	X	X	X	X	X	X	X
Uroflowmetry		X																
Medical history of prostate cancer		X																
Grading of functional digestive, urinary and sexual symptoms (NCI-CTCAE V4.03)		X		X	X	X		X	X	X	X	X	X	X	X	X	X	X
QUESTIONNAIRES																		
QLQ-C30 and QLQ-PR25		X							X		X	X	X	X	X	X	X	X
IPSS		X						X	X		X	X	X	X	X	X	X	X
IIEF5		X						X	X		X	X	X	X	X	X	X	X
LABORATORY TESTS																		
CBC, platelets		X																
PT, PTT, and INR		X																
PSA		X						X		X	X	X	X	X	X	X	X	X
PATHOLOGICAL EVALUATION																		
Gleason score; number of positive biopsies, total number of biopsies; total length of cancer on biopsies; total length of biopsies	X																	
PARACLINICAL INVESTIGATION																		
Multi-parametric MRI (pelvic and prostate)	X[2]								X		X		X		X	X	X	X
Choline PET scan	X[3]																	
TNM evaluation	X																	
TRANSLATIONAL RESEARCH																		
Prostrate tumor biopsies (Initial before any treatment and at recurrence before SBRT)		X[6]																

1.Patient will be contacted by phone 14 weeks after starting SBRT to assess toxicity; an additional visit may be scheduled if required; 2 .Before inclusion, during regular follow-up and in case of biochemical recurrence after SBRT; 3 .Before inclusion and in case of biochemical recurrence after SBRT; 4.Patient's height will only be measured at the screening visit; 5. If not done at the screening visit.; 6.Only applicable for patients who have consented to participate in the biological ancillary study (see section 8.)

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GETUG-AFU 31: a phase I/II multi-center study evaluating the efficacy of repeat stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation therapy.

Appendix: statistical model, simulation study

Statistical considerations

A TITE-CRM method with an empiric dose-toxicity model in a Bayesian framework will be used for the dose-finding part of the trial to identify the recommended dose. The target dose-limiting toxicity (DLT) probability is set at p(DLT)=0.25. Three dose levels of SBRT are to be considered: 5 x 5 Gy (DL-1), 5 x 6 Gy (DL1), 6 x 6 Gy (DL2). The starting dose level is 5 x 6 Gy and dose level 5 x 5 Gy will be explored in case of DLT at the starting dose level. DLTs are evaluated during the 18 weeks following the initiation of salvage-SBRT. Observations of patients who have no DLT at the time of the analysis but have not completed the DLT assessment period will be down-weighted in the likelihood, proportionally to the length of follow up.

The Phase I part of the study will include 3 patients at the first dose level. Radiation dose levels for further patients will be defined based on the estimate of the probability of DLT at each dose-level considering all available information accumulated so far. Patients will be treated at the best current estimate of the recommended dose i.e. the dose associated with an estimated probability of DLT the closest to the target 0.25. Patients may eventually be treated at a dose below the dose recommended by the model for safety reasons. The patients can be recruited with no minimal time interval between successive inclusions. Two additional rules will be applied during dose escalation: no dose skipping and no escalation if at least 1 DLT is observed in the last 3 patients.
The dose-escalation part of the study will terminate once 10 patients have been treated and evaluated at a dose currently identified as the recommended dose. Further patients will then be accrued in the expansion cohort, where toxicity data collected over the first 18-week period and DLT assessment will be analyzed approximately every 10 patients with the possibility of modification of the recommended dose, based on model-based estimates.
The Phase II part of the study will need to include 44 patients, including the patients recruited in the dose-finding part of the phase I allocated at the dose level finally identified as the recommended dose. Thus, a minimal sample size of 47 patients will be required in this Phase I/II study (in the case of inclusion of 44 patients at dose level 2 + 3 patients at dose level 1).

Statistical model for dose escalation

A one-parameter empirical power model will be used to assess the relation between the dose level and the probability of DLT: $F(d,\alpha) = p_d^{\exp(\alpha)}$ where $F(d,\alpha)$ is the estimated probability of DLT at dose-level d, p_d is the prior probability of DLT at dose level d, and α is the unknown parameter to be estimated by the model. The vector $\{p_{0d}\}$ represent the initial guesses of toxicity probabilities, reflecting the clinicians' prior belief. The skeleton of initial guesses of toxicity probabilities $\{p_{0d}\}$ is numerically calibrated using the Lee and Cheung approach (ref ClinTrials 2009) and using the getprior function of R, ensuring good design's operating characteristics. After discussion with the clinicians, the delta defining the indifference interval was set at 0.05 (p(DLT)=0.25 +/- 0.05, i.e. indifference interval: 0.20 to 0.30) and the prior MTD (MTD_0) at the 2nd dose level, meaning that the clinicians believe, a priori, that the 2nd dose (6 x 6 Gy) is probably the MTD. This yields a vector of prior probabilities $\{p_{0k}\}$ equal to 0.08, 0.16 and 0.25 for dose level -1 (5 x 5Gy), dose level 1 (5 x 6 Gy) and dose level 2 (6 x 6 Gy). The clinicians confirmed that it was in accordance with their initial guesses. A non-informative prior distribution Normal (0, 1.34) has been assigned for α in the Bayesian

computation. The simulation study below confirmed that the operating characteristics and the behavior of the model defined with these parameters were reasonable.

Operating characteristics:

The operating characteristics of the proposed design were evaluated using the R titesim function written by Cheung, and considering six different scenarios:

- highly toxic,
- moderately toxic at dose levels -1 and 1, highly toxic at dose level 2
- moderately toxic et every dose level,
- similar with prior probabilities,
- close to the probabilities but a little less toxic,
- little toxic

For the simulation study, we considered that the trial would recruit 47 patients, which is the minimal sample size required in this Phase I/II study.
The following rules were implemented: no dose skipping in escalation, and no escalation if >1 DLT observed among < 3 patients.
For each case, 1000 trials were simulated. The Monte Carlo estimation of the percentage of dose selection, the average number of patients treated at each dose level, the average number of observed DLTs at each dose level demonstrated that the modified CRM design can efficiently identify the MTD, with a reasonable probability of overdosing, and expose few patients to toxicity.
A second set of simulations was performed considering a sample size of 13 patients, which is the minimal expected recruitment in the Phase I part of the study. As expected, the performance is much better when the reassessment is continued during the expansion phase (Phase II part). This is one of the advantages of the CRM method.

Figure 1: Scenarios studied

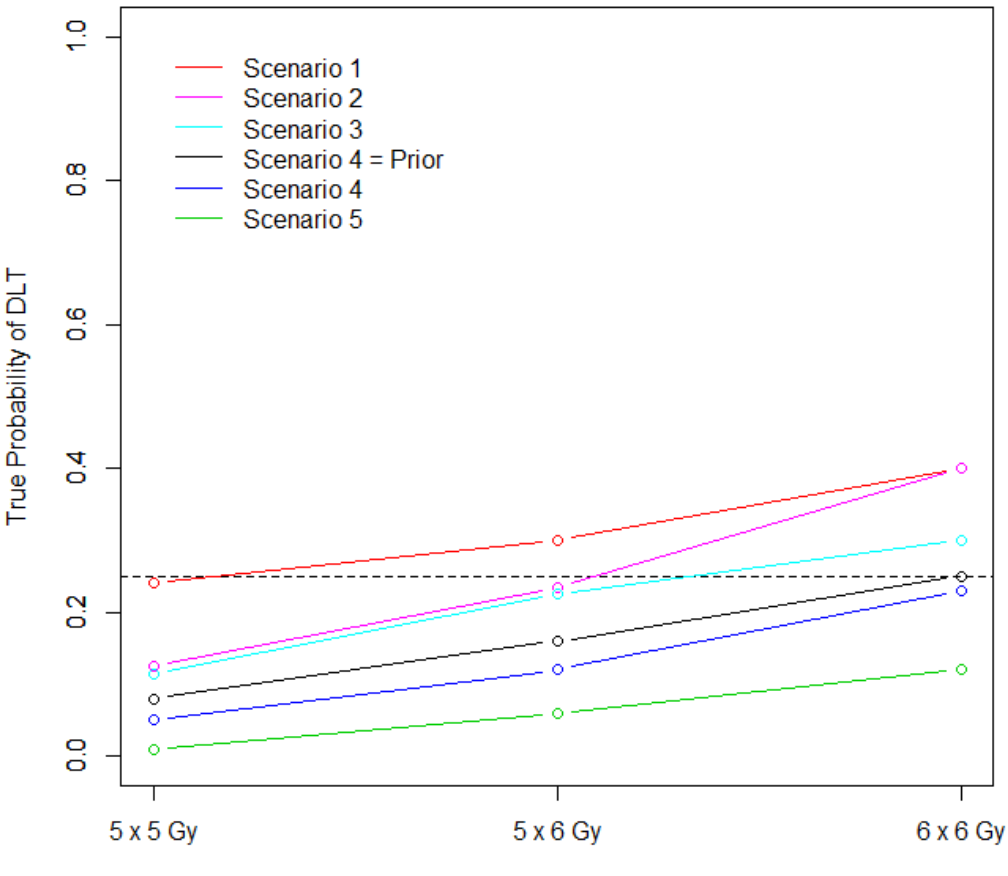

Table 1 : Operating characteristics for five different scenarios for the probability of DLT per dose

1a – Simulation for a recruitment of 47 patients (minimal sample size required in this Phase I/II study)

The grey row represents the true MTD (proba(DLT) closest to the target of 0.25.

SCENARIO 1 : highly toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.24	0.57	23.7	5.7	0.12
1 (5 x 6 Gy)	0.30	0.37	13.4	4.0	0.085
2 (6 x 6 Gy)	0.40	0.06	9.9	4.0	0.085

Expected number of DLTs over the whole trial (47 patients) = 13.7 / trial; 29% patients

SCENARIO 2: moderately toxic at dose levels -1 and 1, highly toxic at dose level 2

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.12	0.12	10.9	1.3	0.03
1 (5 x 6 Gy)	0.23	0.69	21.7	5.1	0.11
2 (6 x 6 Gy)	0.40	0.19	14.4	5.8	0.12

Expected number of DLTs over the whole trial (47 patients) = 12.1 / trial; 26% patients

SCENARIO 3: moderately toxic at every dose level

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.12	0.08	8.0	1.0	0.02
1 (5 x 6 Gy)	0.23	0.52	17.0	3.9	0.08
2 (6 x 6 Gy)	0.30	0.40	22.0	6.7	0.14

Expected number of DLTs over the whole trial (47 patients) = 11.6 / trial; 24% patients

SCENARIO 4 : true proba(DLT) = prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.08	0.006	3.2	0.3	0.01
1 (5 x 6 Gy)	0.16	0.22	11.3	1.8	0.04
2 (6 x 6 Gy)	0.25	0.78	32.5	8.2	0.17

Expected number of DLTs over the whole trial (47 patients) = 10.3 / trial; 22% patients

SCENARIO 5: little less toxic than prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.05	0.001	2.2	0.1	0.002
1 (5 x 6 Gy)	0.12	0.09	8.4	1.0	0.02
2 (6 x 6 Gy)	0.23	0.91	36.4	8.4	0.18

Expected number of DLTs over the whole trial (47 patients) = 9.5 / trial; 20% patients

SCENARIO 6: little toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.01	0	0.8	0.003	<0.001
1 (5 x 6 Gy)	0.06	0	2.3	0.1	0.002
2 (6 x 6 Gy)	0.12	1.0	43.9	5.3	0.113

Expected number of DLTs over the whole trial (47 patients) = 5.4 / trial; 11.5% patients

*% of DLT: mean n. of DLT / total number of patients

1b – Simulation for a recruitment of 13 patients (minimal sample size required in the Phase I part of the study)

The grey row represents the true MTD (proba(DLT) closest to the target of 0.25.

SCENARIO 1 : highly toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.24	0.52	4.7	1.1	0.08
1 (5 x 6 Gy)	0.30	0.27	2.7	0.8	0.06
2 (6 x 6 Gy)	0.40	0.21	5.6	2.2	0.17

Expected number of DLTs over the whole trial (13 patients) = 4.1 / trial; 31% patients

SCENARIO 2: moderately toxic at dose levels -1 and 1, highly toxic at dose level 2

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.12	0.30	3.8	0.5	0.04
1 (5 x 6 Gy)	0.23	0.39	3.2	0.7	0.05
2 (6 x 6 Gy)	0.40	0.31	6.0	2.4	0.19

Expected number of DLTs over the whole trial (13 patients) = 3.6 / trial; 28% patients

SCENARIO 3: moderately toxic at every dose level

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.12	0.21	3.0	0.4	0.03
1 (5 x 6 Gy)	0.23	0.33	3.0	0.7	0.05
2 (6 x 6 Gy)	0.30	0.46	7.0	2.1	0.17

Expected number of DLTs over the whole trial (13 patients) = 3.2 / trial; 25% patients

SCENARIO 4 : true proba(DLT) = prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.08	0.09	2.1	0.2	0.02
1 (5 x 6 Gy)	0.16	0.27	2.8	0.5	0.04
2 (6 x 6 Gy)	0.25	0.64	8.0	2.0	0.15

Expected number of DLTs over the whole trial (13 patients) = 2.7 / trial; 21% patients

SCENARIO 5: little less toxic than prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.05	0.05	1.6	0.1	0.01
1 (5 x 6 Gy)	0.12	0.21	2.7	0.3	0.02
2 (6 x 6 Gy)	0.23	0.74	8.7	2.0	0.15

Expected number of DLTs over the whole trial (13 patients) = 2.4 / trial; 18% patients

SCENARIO 6: little toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.01	0.004	0.6	0.01	0.001
1 (5 x 6 Gy)	0.06	0.04	1.8	0.09	0.007
2 (6 x 6 Gy)	0.12	0.96	10.6	1.3	0.10

Expected number of DLTs over the whole trial (13 patients) = 1.4 / trial; 11% patients

*% of DLT: mean n. of DLT / total number of patients

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

Section/item	ItemNo	Description	Protocol Page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Phase I/II Multi-center Study Evaluating the Efficacy of Repeat Stereotactic Radiation in Patients With Intraprostatic Tumor Recurrence After External Radiation Therapy (STEREO-RE-PRO)	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ClinicalTrials : NCT03438552	2
	2b	All items from the World Health Organization Trial Registration Data Set IdRCB : 2017-A00008-45	2
Protocol version	3	Date and version identifier version n°2.0 06/10/2017	1
Funding	4	Sources and types of financial material, and other support Support by a grant of National Institute of Cancer (INCA)	Not explicitly mentioned in the protocol
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Docteur David PASQUIER Centre Oscar Lambret - Département de Radiothérapie 3, rue Fréderic Combemale - BP307 59020 Lille Cedex Tél : 03.20.29.59.11 - Fax : 03.20.29.58.96 E-mail : d-pasquier@o-lambret.fr	2

	5b	Name and contact information for the trial sponsor **UNICANCER** 101 Rue de Tolbiac, 75654 Paris Soazig NENAN +33 (0)185 343 113 s-nenan@unicancer.fr Meryem BRIHOUM +33 (0)1 80 50 12 95 m-brihoum@unicancer.fr	1-2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	46; 49
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	42-44; 46
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	17-22
	6b	Explanation for choice of comparators	Not applicable

Objectives	7	Specific objectives or hypotheses **Primary objective** : Selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity observed during the 18 weeks following the initiation of salvage-SBRT. Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate **Secondary objectives** Evaluation of acute and late genitourinary toxicities of the salvage-SBRT Estimate the efficacy of the salvage-SBRT in terms of clinical progression-free survival and overall survival Evaluation of Quality of life after salvage-SBRT	22-23
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Study Type: Interventional Primary Purpose: Treatment Intervention Model: Sequential Assignment Number of Arms: 3 Masking: Open Label Endpoint Classification: Safety/Efficacy Study Enrollment: 47	4

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Centers are hospitals and clinics (see below) : Centre François Baclesse, Caen, France Principal Investigator: Marlon SILVA Centre Jean Perrin, Clermont-Ferrand, France Principal Investigator: Geneviève LOOS Centre George François Leclerc, Dijon, France Principal Investigator: Gilles CREHANGE Centre Oscar Lambret, Lille, France Principal Investigator: David PASQUIER Centre Léon Bérard, Lyon, France Principal Investigator: Pascal Pommier Institut régional du Cancer de Montpellier, Montpellier, France Principal Investigator: David AZRIA Groupe Hospitalier Pitié-Salpétrière, Paris, France Principal Investigator: Philippe MAINGON ICO -Site René Gauducheau, Saint-Herblain, France Principal Investigator: Stephane SUPIOT Institut de Cancérologie Lucien Neuwirth, Saint-Priest-en-Jarez, France Principal Investigator: Nicolas MAGNE	Additional form (not in the protocol)

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	26-27

Minimum Age: 18 Years
Gender: Male
Accepts Healthy Volunteers?: No

Inclusion Criteria:

1. Biochemical recurrence occurring at least 2 years after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL)
2. T1-T2c and PSA ≤20 ng/mL and Gleason score ≤7 at initial diagnosis of prostate cancer before the initial/first treatment.
3. Recurrence of prostatic adenocarcinoma proven by histology following radiotherapy by transrectal or transperineal sextant biopsies of the two lobes of the prostate, with a minimum of 12 biopsies, irrespective of Gleason score. Biopsies of the seminal vesicles are optional.
4. Clinical stage T1-T2 on relapse; unilateral extracapsular extension (T3a) on MRI permitted except posteriorly relative to the rectum
5. Estimated clinical target volume (CTV) / prostate volume < 0.5 based on imaging and biopsies
6. Pelvic and prostatic assessment by multiparametric MRI-Absence of pelvic or metastatic recurrence proven by choline PET scan
7. Performance status WHO 0-1
8. PSA level ≤10 ng/mL at baseline (before salvage-SBRT)
9. PSA doubling time >10 months
10. International Prostate Cancer Score (IPSS) ≤12
11. Uroflowmetry with a maximum flow rate >10 mL/s, a postvoid residual urine volume <150 mL, and a urine volume >150 mL.
12. No other anti-cancer treatment since the external radiotherapy administered as first-line treatment
13. No other anti-cancer treatment planned for the current recurrence
14. No contraindication to fiducial marker implants; haemostatic disorders must be corrected before implantation
15. Age >18 years
16. Life-expectancy greater than or equal to 5 years (Lee scale)
17. Patient registered with a health insurance system
18. Patient who has signed the informed consent form
19. Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests, and other study procedures indicated in the protocol.

Exclusion Criteria:

1. Lymph node or metastatic spread
2. Late post-radiotherapy urinary or gastrointestinal toxicity of grade ≥2 (following primary radiotherapy)
3. Other cancers in the last 5 years except for non-melanoma-type skin cancer
4. History of inflammatory bowel disease
5. Anticoagulant treatment
6. Contraindications to undergoing MRI
7. Prostate volume >80 cc
8. Transurethral resection of the prostate (TURP) in the 6 months before registrations
9. Presence of rectal telangiectasia grade 3 classified by the Vienne Rectoscopy Score (obligatory rectoscopy)
10. Previous rectal surgery
11. Patients unable to undergo medical follow-up in the study for geographical, social or psychological
12. Person deprived of their liberty or under protective custody or guardianship
13. Patients enrolled in another therapeutic study

All patients during the SBRT planning with a ratio of clinical target volume (CTV) / prostate volume > 0.5 will be withdrawn from the study. These patients will be considered as not evaluable and will

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	28-30
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) Not applicable	31
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Not applicable	31
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Concomitant treatment permitted : any treatment considered necessary for the health of the patient	31
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Primary Outcome Measure:** [Time Frame: 18 weeks] Selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity observed during the 18 weeks following the initiation of salvage-SBRT. The dose-escalation part of the study will terminate once 10 patients have been treated and evaluated at a dose currently identified as the recommended dose. [Time Frame: 6 years] Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate **Secondary Outcome Measure:** 1. Time Frame: 3 years] Evaluation of acute and late genitourinary toxicities of the salvage-SBRT 2. [Time Frame: 6 years] Estimate the efficacy of the salvage-SBRT in terms of clinical progression-free survival and overall survival 3. [Time Frame: 6 years] Evaluation of Quality of life after salvage-SBRT	23-24

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	24-25; 31-35
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations At least 47 patients **Sample Size Calculations**	39-40
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Communication and follow-up of the participating centers	44; 50
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions TITE-CRM	25; 39-40
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned Number of inclusion attributed directly by eCRF	25
Implementation	16c	Who will generate the allocation sequence: computer/eCRF by inclusion program. Biostatistician who will enrol participants: Investigator. and who will assign participants to interventions: Biostatistician.	25
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how Not applicable	Not applicable

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Not applicable	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Describe in protocol and data management procedures	30; 31-35; 43-44
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols Describe in protocol and data management procedures	31; 31-35
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Describe in protocol and data management procedures	30; 43-44
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	41-42
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) Not applicable	41-42
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Not applicable	41-42
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Coordinator : validate the risk analysis (LIR) and the monitoring plan Project Manager : determine the risk analysis (LIR) and write the monitoring plan Clinical Research Associate (CRA) :perform monitoring according the monitoring plan	42
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	42
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct This point is provided by the vigilance unit of the sponsor. All details are described in the protocol	35-38
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Actually and according the risk analysis, no audit is planned	44
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval N° IdRCB : 2017-A00008-45 Initial Approval by CPP Nord-Ouest I (Committee for the Protection of Personnes/Ethic committee) : 25/07/2017 Approval Number: CPP3517-I	45

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) Each major protocol amendment is submitted to authorities for approval. After approval, it is communicated to all the actors of this project (investigators, trial centers, trial registry ….)	46
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Principal Investigator or sub-investigator	47
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Not applicable	33; 38; 48
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Collected by investigators and CRA on each trial centers. These data are anonymized. Shared on the eCRF. There is a control access on the eCRF	43; 47-49
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site None	Not applicable
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Directly on the eCRF	48-49
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation Not applicable	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions A publication is planned; no publication restriction.	50

	31b	Authorship eligibility guidelines and any intended use of professional writers Coordinator will be the first author; co investigators will be authors.	50
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code N/A	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional form (not in the protocol)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable Not applicable	59

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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GETUG-AFU 31: a phase I/II multi-center study evaluating the safety and efficacy of salvage stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation therapy; study protocol

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GETUG-AFU 31: a phase I/II multi-center study evaluating the safety and efficacy of salvage stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation therapy; study protocol

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ABSTRACT

Introduction. Prostate cancer is the third most important cancer in terms of mortality in men. No standard local treatment exists for patients with an intraprostatic recurrence after radiotherapy. Stereotatic body radiotherapy (SBRT) could be a curative treatment for local recurrence. The phase I/II primary objective is the selection of the recommended dose for salvage-SBRT and to estimate the efficacy.

Methods and Analysis. We plan to perform a multicenter prospective phase I/II study including at least 47 patients. Eligible patients are patients with biochemical recurrence occurring at least 2 years after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL) and histologically proven intraprostatic recurrence only (stage T1-T2 on relapse, PSA level ≤10 ng/mL, PSA doubling time >10 months, absence of pelvic or metastatic recurrence proven by choline or PSMA PET-scan, and pelvic and prostatic assessment by multiparametric MRI).

The phase I primary objective is the selection of the recommended dose for salvage-SBRT (5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity. The dose of salvage-SBRT will be selected using a Time-to-Event Continual-Reassessment-Method based on dose-limiting toxicity defined as grade ≥3 gastrointestinal or urinary toxicity or any other grade 4 adverse event. The phase II primary outcome is to estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate (Phoenix definition: increase in serum total PSA ≥2 ng/mL above the nadir). Phase II secondary outcomes are acute and late toxicities, quality of life, clinical progression-free survival defined as the time interval between the date of registration and the date of clinical progression or death irrespective of the cause.

Ethics and Dissemination. The study has received ethical approval from the Ethics committee "Ile-de-France III". Academic dissemination will occur through publication and conference presentations.

Trial registration: NCT03438552

Date of trial registration: November 14, 2017

Strengths and limitations of this study funding

- Very innovative trial evaluating stereotactic body radiotherapy for recurrent prostate cancer, the only ongoing trial of this kind in Europe to our knowledge
- Clinical trial supported by the GETUG-AFU cooperative group, expert in the field
- Time-to-Event Continual Reassessment Method, a more appropriate method than the 3+3 design to quantify late toxicity in phase I radiotherapy trials
- Proof-of-concept study; further research will be required
- Small sample size

Keywords: prostate cancer, stereotactic body radiation therapy, recurrent prostate cancer

Background

Prostate cancer is the third most important cancer in terms of mortality in men (after lung and colorectal cancer), and the fourth leading cancer overall [1]. In the European Union, it was predicted that 72600 patients would die from prostate cancer in 2015. The rate of recurrence/relapse of prostate cancer after primary external beam radiotherapy varies from 21% to 65% depending on the study [2,3]. Zelefsky et al. performed biopsies on 339 patients after treatment with 3-dimensional conformal radiotherapy (3D-CRT) or intensity modulated RT for T1c-T3 stage prostate cancer, with a minimum follow-up of 2.5 years [2]. They found that the rate of positive biopsy according to radiation dose was 65% for <70.2 Gy, 38% for 70.2 Gy, 27% for 75.6 Gy, and 25% for ≥81 Gy. A two years biopsy was performed in 312/843 patients included in MRC RT01 trial. A positive biopsy was prognostic of worse biological progression free survival compared with negative and suspicious biopsies, hazard ratio (HR)=4.81 (95% confidence interval [CI]: 2.50-9.26, p<0.001). The estimate for survival was HR=1.58 (95% CI: 0.52-4.78, p=0.42).

In the literature and guidelines a minimum time of two years is recommended between radiotherapy and prostate biopsies to minimize the risk of false positive and this two-year interval has been selected in our study. This risk decreases over time. Nevertheless the guidelines recommend to perform prostate biopsies before any salvage treatment, and the diagnosis is based on imaging too in our study.

D'Amico reported that the 5-year prostate cancer mortality rate after biochemical recurrence in patients who received external beam radiotherapy for localized prostate cancer depended on the pretreatment Gleason score: 24% for ≤6 score, 40% for 3+4 score, and 59% for 4+3 or higher score (p=0.01); as well as, on the pretreatment PSA level: 22% for ≤10 ng/mL, 40% for >10 and ≤20 ng/mL, and 60% for >20 ng/mL (p=0.04) [4]. In addition, Buyyounouski reported that the interval to biochemical recurrence was an important factor in identifying men at high risk of distant metastasis and death [5]. An interval to biochemical recurrence (PSA nadir + 2 ng/mL) of <18 vs. ≥18 months was associated with a 5-year distant metastasis rate of 52% vs. 20% (p<0.0001), and a prostate-cancer

specific mortality rate of 36% vs. 6% (p=0.0001). Thus late relapse and long PSA doubling time are prognostic factors of solely intraprostatic relapse.

Prostate-specific antigen (PSA) is a validated biomarker for prostate cancer. PSA levels are extensively used to monitor response to radical prostatectomy (RP) and external-beam radiotherapy (EBRT). The serum PSA level is an important surrogate for recurrence in prostate cancer patients. The recommendations of the Radiation Therapy Oncology Group (RTOG) ASTRO Phoenix Consensus Conference suggested that an increase of ≥2 ng/mL from the nadir be used to define recurrence/relapse [6]. It is important to note that biochemical recurrence may indicate local or systemic disease recurrence, and may require prostate biopsy for confirmation particularly when local salvage treatments are being considered [7].

A number of different salvage treatments have been used after failure of primary radiotherapy. RP is more invasive than brachytherapy, ultrasound, high-intensity focused ultrasound (HIFU), and SBRT. Below is a brief discussion of the results obtained with each techniques and its associated toxicity and complications.

Salvage RP (SRP) is a treatment option after local recurrence following EBRT. However, the morbidity, including incontinence and erectile dysfunction, is higher than that observed with first-line RP patients. A systematic literature review [7] reported that the probability of biochemical relapse–free survival (bRFS) following SRP in prostate cancer patients was 47-82% after 5 years and 28-53% after 10 years. SRP has an increased risk of adverse events due to fibrosis and poor wound healing after radiotherapy. Furthermore, SRP after radiotherapy compared to primary RP has a significantly higher rate of urinary and gastrointestinal morbidity [8]. The review above [7], reported that the most frequent complications were anastomotic stricture (7-41%) and rectal injury (0-28%). The majority (50-91%) of men had erectile dysfunction before SRP and 80-100% after surgery. Post-operative urinary continence ranged from 21-90%.

In a recent review, salvage brachytherapy after EBRT is reported to achieve biochemical control rates of 20% to 89% (median follow-up: 19 to 108 months) [9]. Rates of genitourinary toxicities range

from 12% to 87% for grade 1-2, and 3% to 47% for grade 3-4 toxicities. Similarly, the rates of gastrointestinal toxicities range from 4% to 65% for grade 1-2, and 0% to 20% for grade 3-4 toxicities. Erectile dysfunction was observed in 2% to 95% of men. A phase II study of salvage high-dose-rate brachytherapy (HDR) for treating recurrent prostate cancer after definitive external beam radiotherapy was reported by Yamada [10]. The 42 patients enrolled, with biopsy proven recurrence, were treated with salvage HDR (iridium-192) with a resulting bRFS at 5 years of 68.5% (median follow-up of 36 months [range: 2-66 months]). Acute genitourinary toxicity was observed: grade 1, 38% of patients and grade 2: 40%. Similarly, late genitourinary toxicity was observed: grade 1, 38% of patients and grade 2, 48%. In addition, 1 patient had a grade 3 urinary incontinence and 3 had grade 3 urethral strictures. Late gastrointestinal toxicities were observed: grade 1, 43% of patients and grade 2, 14%. More recently, a study of 83 prostate cancer patients with local recurrence after radiotherapy treated with high-dose-rate brachytherapy was reported [11]. The 3-year and 5-year bRFS were 76% and 67%. A phase II study of the RTOG in 100 patients was recently presented: twelve (14%) experienced late grade 3 genitourinary/gastrointestinal adverse effects. This rate of late grade 3 toxicity (14%) was not unacceptable by the predetermined protocol specification, without any grade 4-5 events. The only factor predictive of late toxicity was implant dose, underlining the need for meticulous planning and technique to limit the final delivered dose [12]. In France, a phase II study, “Brachytherapy for Recurrent Prostate Cancer” (CAPRICUR) was recently completed [13].

HIFU is another less invasive salvage treatments following recurrence. HIFU uses focused ultrasound to generate heat (85°C) which induces tissue necrosis [14]. The following studies have investigated the use of salvage-HIFU after initial radiotherapy. A French group treated 290 men with biopsy-confirmed recurrent prostate cancer, after radiotherapy, with salvage HIFU [15]. At 7 years, the cancer-specific survival rate was 80% and the metastasis-free survival rate was 79.6%. Recto-urethral fistula occurred in 0.4% of patients and 19.5% had grade 2/3 incontinence. Half of the patients also received hormone therapy. Survival without relapse at 5 years after HIFU, by D’Amico risk groups prior to their initial treatment, was 45% (favorable), 31% (intermediate risk) and 21% (high risk). In this

cohort, the grade ≤3 urinary incontinence levels were 23% (favorable), 14% (intermediate risk) and 9% (high risk). Nearly 8% of patients required an artificial sphincter following HIFU. Importantly, pubic osteitis occurred in 2.5% of patients despite adherence to parameters specific to HIFU following radiotherapy [15].

Cryotherapy is thermo-ablative treatment; the third–generation argon/helium-based cryotherapy system creates precise isotherms through ultrathin needles [16]. In a retrospective multicenter series pooling 279 patients, survival without biochemical relapse at 5 years was 54%. Prostatic biopsies showed tumor persistence in 32% of patients following cryotherapy [17]. In a paired case-controlled study, prostatectomy and cryotherapy were compared following radiotherapy. Survival without relapse (PSA nadir + 0.4 ng/mL) at 5 years was significantly lower after cryotherapy (21% vs. 61%, p<0.001); this was confirmed by the 5-year OS rate of 85%, cryotherapy, vs 95%, radical prostatectomy (p=0.001) [18]. Intermediate results from a study investigating third-generation cryotherapy as a salvage treatment of locally recurrent prostate cancer after radiotherapy was published [19]. The 5-year bRFS rate (Phoenix definition) was 43.5% and with a 5-year OS rate of 92.3%. Mild complications (grades 1 and 2) were reported including: mild incontinence (9.4%), acute rectal pain (31.3%), lower urinary tract symptoms (15.6%) and erectile dysfunction (57.1%). Grade 3 toxicities: incontinence (3.1%) and urethral sloughing (3.1%) were observed.

Androgen-deprivation therapy (ADT) alone (continuous or intermittent) is commonly given to patients with biochemical relapse after radiotherapy [20]. In a series based on data from a North American national registry (CaPSURE), 71% of patients were treated for biochemical relapse after prostatectomy or radiotherapy. ADT was initiated in 93% of these patients, and the remaining patients were treated with surgery, brachytherapy, cryotherapy, or repeat external radiotherapy [21]. ADT may cause adverse effects impacting patient's quality of life (including: hot flushes, erectile dysfunction and reduced libido, cognitive impairment, and anemia). The metabolic changes associated with hormone therapy may also increase the risk of cardiovascular morbidity. The reduction in bone mass is maximal in the first year and increases with the duration of castration; the risk of fracture is increased in patients

surviving for more than 5 years [22-23]. The guidelines suggest that a simple follow-up can be implemented for local recurrence in patients with a limited life expectancy or for those who do not wish to undergo local salvage treatment. The last European Association of Urology guidelines [24] recommended to perform salvage surgery in experienced centres due to the increased rate of side effects. It is recommended to offer/discuss HIFU, cryosurgical ablation and salvage brachytherapy to/with patients without evidence of metastasis and with histologically proven local recurrence and to inform patients about the experimental nature of these approaches. The level of evidence for each of these recommendations is 3 [24].

SBRT delivers highly conformal, high-dose radiation in a few fractions (hypofractionation), typically 5 to 7 fractions for prostate cancer. It is reported that tissues with a low α/β ratio, as for prostate cancer, are more sensitive to large doses of radiation per fraction. The surrounding normal tissue could have similar or higher α/β ratio. This suggests that hypofractionation (large radiation dose per fraction) may result in improved tumor control with limited toxicity. A pooled analysis of 1100 patients included in separate prospective phase II studies in 8 institutions was performed to evaluate the effectiveness of SBRT as a first-line treatment for localized prostate cancer [25]. The SBRT was delivered by CyberKnife with a median dose of 36.25 Gy in 4-5 fractions. The 5-year bRFS rate was 93% for all patients. Thus relapse-free survival rates after SBRT compare favourably with other definitive treatments for low and intermediate-risk patients with a short follow up. SBRT is well tolerated with a low effect on quality of life [25-28]. In addition sexual function appeared to be spared in the majority of patients [25-28].

SBRT has also been used as a salvage treatment following failure of external radiotherapy. Jereczek-Fossa et al. published data on 34 consecutive patients treated with robotic SBRT for isolated recurrent primary, lymph node, or metastatic prostate cancer [29]. Of the 34 patients, 15 patients had intraprostatic recurrence, confirmed by biopsy, and were treated with SBRT (CyberKnife) with a median dose of 30 Gy in 5 fractions. Fourteen patients showed a biochemical response; the median survival without recurrence was 13 months. Five patients presented a clinical relapse, including one

new intraprostatic recurrence. Urinary toxicity was low, with a grade 3 urinary toxicity in only one patient. No case of acute or late gastrointestinal toxicity was reported. This good gastrointestinal tolerability has subsequently been confirmed [29-32]. In Fuller et al twenty-nine patients were treated in a phase II trial with stereotactic radiotherapy for intraprostatic recurrence [30]. Eligible patients had to present biopsy-proven intraprostatic recurrence graded T1 to T3N0M0 more than 2 years post-radiotherapy and without a pre-existing grade >1 radiotherapy toxicity. The prior median dose delivered was 73.8 Gy and the median interval between the treatments was 88 months. The dose delivered to the entire gland was 34 Gy in five fractions over 5 days (heterogeneous intraprostatic dose of up to 50 Gy). With a median follow-up of 24 months, survival without recurrence was 82%. Toxicity was acceptable, with 18% grade ≥2 urinary toxicity, including one patient with a grade 4 toxicity, and no late gastrointestinal toxicity above grade 1. Particular attention should be given to patients who still exhibit urinary toxicity after initial radiotherapy [30]. Our preliminary retrospective results in 23 patients treated for this indication were published recently [31]. A total dose of 36 Gy was prescribed in 6 fractions of 6 Gy. Nineteen patients had a whole-gland and four a partial treatment. Median follow-up was 23 months (range 6 to 40 months). We observed no grade 4 or 5 toxicity. Two patients presented grade 3 toxicities. Others toxicities include urinary (5 grade 2 and 9 grade 1) and rectal toxicities (2 grade 2 and 2 grade 1). The dose levels selected in our study are close to those used in de novo patients, and the same as those described in retrospective salvage treatment series. These schemes seem to provide an acceptable compromise between efficacy and toxicity but have not been evaluated prospectively.

To date, no standard local treatment exists for patients with an intraprostatic recurrence after radiotherapy [33]. A number of treatments options exist including: radical prostatectomy, brachytherapy, HIFU, cryotherapy, and stereotactic radiotherapy. The literature to date consists mainly of retrospective and small prospective series making it difficult to assess and compare these techniques. In recent years, SBRT has been used to treat localized prostate cancer in the primary setting but also as a salvage treatment after failure of radiotherapy. The initial results of these

retrospective studies are promising, with respect to survival and tolerance, but further studies are required to confirm these initial results. Our proposed study will provide further evidence of SBRT as a supplementary non-invasive curative treatment for local recurrence following radiotherapy. This study could provide the foundation for prospective studies comparing the available salvage treatments after radiotherapy.

Methods/design

This study is approved by the Ethics committee "Ile de France III" (2017-A00008-45) and is registered on clinicaltrials.gov (NCT03438552). This multicenter open-labelled phase I/II study will initially select the SBRT scheme (phase I), either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy. The effectiveness of SBRT scheme selected in phase I will then be evaluated in a single-arm multicenter phase II study.

PHASE I primary objective and assessment:

Selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity observed during the 18 weeks following the initiation of salvage-SBRT. The dose of salvage-SBRT will be selected using a Time-to-Event Continual Reassessment Method [34-36] based on dose-limiting toxicity defined as grade ≥3 gastrointestinal or urinary toxicity or any other grade 4 adverse event observed during the 18 weeks following the initiation of salvage-SBRT.

PHASE II primary objective and assessment:

Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate (Phoenix definition: increase in serum total PSA ≥2 ng/mL above the nadir). Time to biochemical relapse-free survival will be computed from registration. Patients alive without biochemical progression at the time of the analysis will be censored at the last follow-up date. In the event of death, whatever the cause of death, the patient will be considered as a failure.

PHASE II secondary objective(s) and assessment:

- Acute and late genitourinary and gastrointestinal toxicities over the first 3 years according to the NCI-CTCAE V4.03 classification (June 14th, 2010), International prostate Symptom Score (IPSS) score for urinary symptoms, and International Index of Erectile Function (IIEF5) for erectile function. Patients will be followed for 5 years after salvage SBRT to assess late toxicity. Patients with second biochemical recurrence will not be excluded in order to assess late toxicity.
- Quality of life will be evaluated based on the EORTC QLQ-C30 and QLQ-PR25 scales. The Time Until Definitive Deterioration (TUDD) will be computed from registration until the first observation of a definitive deterioration of the quality of life, defined as a score decreased by 10 points (in the case of global health scale and functional scales) or increased by 10 points (in the case of symptom scales) compared to the score at baseline, without later improvement superior to 10 points compared to baseline score.
- Clinical progression-free survival is defined as the time interval between the date of registration and the date of clinical progression (local progression assessed by the physical examination, or appearance of metastatic lesions) or death irrespective of the cause.
- Overall survival is defined as the time interval between the date of registration and the date of death irrespective of the cause.
- Erythroblast transformation-specific related gene (ERG) fusion expression will be evaluated using immunohistochemistry (IHC) tests. ERG fusion and androgen-receptor splice variant 7 (ARV7) expression will be evaluated on biopsies before the first radiotherapy treatment (at diagnosis, if available) and before salvage radiotherapy after biochemical recurrence.

DIAGNOSIS AND INCLUSION CRITERIA:

- Biochemical recurrence occurring at least 2 years after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL)

- T1–T2c and PSA ≤20 ng/mL and Gleason score ≤7 at initial diagnosis of prostate cancer before the initial/first treatment.
- Recurrence of prostatic adenocarcinoma proven by histology following radiotherapy by transrectal or transperineal sextant biopsies of the two lobes of the prostate, with a minimum of 12 biopsies, irrespective of Gleason score. Biopsies of the seminal vesicles are optional.
- Clinical stage T1-T2 on relapse; unilateral extracapsular extension (T3a) on magnetic resonance imaging (MRI) permitted except posteriorly relative to the rectum
- Estimated clinical target volume (CTV) / prostate volume < 0.5 based on imaging and biopsies
- Pelvic and prostatic assessment by multiparametric (mp) MRI
- Absence of pelvic or metastatic recurrence proven by choline positron emission tomography (PET) scan
- Performance status WHO 0-1
- PSA level ≤10 ng/mL at baseline (before salvage-SBRT)
- PSA doubling time >10 months
- IPSS ≤12
- Uroflowmetry with a maximum flow rate >10 mL/s, a postvoid residual urine volume <150 mL, and a urine volume >150 mL.
- No other anti-cancer treatment since the external radiotherapy administered as first-line treatment
- No other anti-cancer treatment planned for the current recurrence
- No contraindication to fiducial marker implants; haemostatic disorders must be corrected before implantation
- Age >18 years

- Life-expectancy greater than or equal to 5 years (Lee scale)
- Patient registered with a health insurance system
- Patient who has signed the informed consent form
- Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests, and other study procedures indicated in the protocol.

EXCLUSION CRITERIA:

- Lymph node or metastatic spread
- Late post-radiotherapy urinary or gastrointestinal toxicity of grade ≥2 (following primary radiotherapy)
- Other cancers in the last 5 years except for non-melanoma-type skin cancer
- History of inflammatory bowel disease
- Anticoagulant treatment
- Contraindications to undergoing MRI
- Prostate volume > 80 cc
- Transurethral resection of the prostate (TURP) in the 6 months before registration
- Presence of rectal telangiectasia grade 3 classified by the Vienne Rectoscopy Score (obligatory rectoscopy) [37,38]
- Previous rectal surgery
- Patients unable to undergo medical follow-up in the study for geographical, social or psychological
- Person deprived of their liberty or under protective

INTERVENTION

A flow chart presenting the different steps from inclusion until treatment is presented in Fig. 1. Five or six fractions, at a level of 5 or 6 Gy per session (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy), will be delivered over a maximum of 12 days to provide a total dose of 25 to 36 Gy. This radiotherapy may be

administered with the CyberKnife® or a linear accelerator allowing stereotactic radiotherapy. The patient will be placed in a stable and reproducible supine position. Intraprostatic markers (fiducials) will be implanted before the dosimetric CT-scan and MRI are performed. The choice of markers is left to the discretion of each participating site (gold seeds, etc.). The site needs to ensure that the repositioning of the prostate is precise (≤2 mm), allowing an exact overlay between dosimetric MRI and computed tomography (CT)-scan. The implant of fiducials is obligatory irrespective of the stereotactic radiotherapy technique used. The fiducials can be implanted during or after the biopsies. The CT-scans and MRIs registration is guided by the fiducials. Each team can choose the fiducials visible on the MRI they wish to use and/or integrate a specific sequence during the centering MRI for better visualization.

An mpMRI and CT-scan will be carried out at least one week after fiducial implantation. CT-scan images should be acquired with the patient in the treatment position using the chosen immobilizing system, if required according to centers' standard procedures. An intravenous injection of a contrast product should be administered unless contraindicated. Acquisition should allow anatomical structures and markers (already implanted in the prostate) to be visualized. The bladder will be half-filled (neither full nor empty, i.e. a final voiding 90 minutes before the CT-scan followed by ingestion of 250-350 mL of water). The rectum will be empty and not distended. If necessary rectal enema can be used before CT-scan acquisition. Contiguous CT-scan slices ≤2 mm thick will be taken between the L5-S1 joint space and the small trochanters. After image transfer to a planimetric console, fiducial-based registration with the prostatic mpMRI will take place in order to provide a better definition of the Gross Target Volume (GTV) and prostatic contours, especially the apex. Fiducial-based CT-MRI registration is mandatory. Multimodality image registration with Choline PET is possible but not mandatory.

Delineation of the target volume will be carried out by a radiotherapist experienced in the definition of prostate volumes on CT-scans and MRIs. The mpMRI-defined contour will be integrated with the CT-scan derived contours in order to define tumor and the prostatic apex more precisely. GTV will be

represented by lesion defined on the multiparametric MRI +/- choline PET; a 5-7 mm margin around the GTV will be used to define the Clinical Target Volume (CTV). CTV is contained in the prostate, except in the case of extracapsular extension (unilateral extracapsular extension on MRI permitted except posteriorly relative to the rectum). In the case where the positive biopsy(ies) are outside and adjacent to the visible lesions on the MRI, the zone containing these biopsies must be included in the CTV so that the prostate cancer recurrence not visible on the MRI is included in the CTV. If no lesion is visible on the MRI and/or choline PET, the zone containing positive biopsies must be included in the CTV. For example: MRI +/-choline PET lesion in 3p and 4p according to ESUR guidelines, with positive biopsies in 1p, 3p and 4p: CTV = MRI GTV + 5 mm + the posterior right base. The total CTV should not be more than half of the total volume of the prostate by MRI. The planning target volume (PTV) will be obtained by an expansion of 2 mm around the CTV in this repeat radiotherapy context. This margin involves that the probability of coverage at 25, 30, or 36 Gy is low, so the reporting will include D2%, 50%, D98% and D95% to describe as much as possible delivered dose. Organs at risk constraints are specified in Table 1. Daily image guided radiation therapy is mandatory, intra fraction tracking is recommended.

Rectum wall	Bladder wall	Urethra + 3 mm
V27 Gy <2 cc	V27 Gy <5 cc	V24 Gy <30%
V12 Gy <20%	V12 Gy <15%	D_{max} (35 mm^3) <39 Gy
		V36 Gy <1 cc

Table 1. Organs at risk constraints

Quality control is particularly important in this setting of repeat radiotherapy. Before starting patient enrolments a “dummy-run” will be conducted: an anonymous clinical chart will be forwarded to all participating sites with clinical, scintigraphy (choline PET-scan), CT-scan and MRI data prior to repositioning. After delineating the relevant volumes, each site will have to perform a dosimetry which will be centralized in order to verify that the constraints are being observed. For each site, the

dosimetric data will be subject to a centralized review prior to SBRT administration in order to verify that constraints are being observed. Follow-up visits are described in Figures 1 and 2.

SAMPLE SIZE CALCULATION

Required number of patients to be included: minimum 47 patients. The total sample size will depend upon the number of patients allocated at the different dose levels in the dose-finding parts of the trial. A minimum of 13 patients will be recruited before the expansion phase is open (Phase II part). A total of 44 patients allocated at the recommended dose (recruited in the dose-escalation stage or in the expansion phase) and evaluable at 3 years are required for the main analysis of the Phase II part of the trial to ensure an 85%-power if 3-year bRFS is p1=0.70, with a test against p0=0.50 at a one-sided 5%-alpha level.

STATISTICAL CONSIDERATIONS

PHASE I

Three dose levels of SBRT are to be considered: 5 x 6 Gy, 6 x 6 Gy, and 5 x 5 Gy. The starting dose level is 5 x 6 Gy. The lower dose level, 5 x 5 Gy, will be considered if excessive toxicity is reported at the first dose-level (5 x 6 Gy). A TImeTo Event-Continuous Reassessment Method (TITE-CRM) with an empiric dose-toxicity model in a Bayesian framework will be used for the dose-finding part of the trial to identify the recommended dose. The target dose limiting toxicity (DLT) probability is set at p(DLT)=0.25. Observations of patients who have no DLT at the time of the analysis but have not completed the DLT assessment period will be down-weighted in the likelihood, proportionally to the length of follow up; for instance, if the last patient has been recruited 8 weeks before a new patient is available for enrolment, and is evaluated at week 10 with no DLT, then his observation is attributed a weight of 10/18=0.56.

At least three patients will be enrolled at the first dose-level and fully evaluated over the 18-week study period before the dose is escalated to the next dose-level. Radiation dose levels for further

patients will be defined based on the estimate of the probability of DLT at each dose-level considering all available information accumulated so far. Patients will be treated at the best current estimate of the recommended dose i.e. the dose associated with an estimated probability of DLT the closest to the target 0.25. Patients may eventually be treated at a dose below the dose recommended by the model for safety reasons. The patients can be recruited with no minimal time interval between successive inclusions. During the dose-escalation part of the trial, safety data will have to be reported in the data base in real time. A monthly teleconference meeting with the participation of the biostatistician, the trial coordinator and a representative of the sponsor, to summarize toxicity observations and define the dose to be allocated to the next patient(s) will be held. Safety data will be discussed with an Independent Data Monitoring Committee (IDMC) at the end of the dose-escalation part of trial, or before if needed.

The dose-escalation part of the study will terminate once 10 patients have been treated and evaluated at a dose currently identified as the recommended dose. Further patients will then be accrued in the expansion cohort, where toxicity data collected over the first 18-week period and DLT assessment will be analyzed approximately every 10 patients with the possibility of modification of the recommended dose, based on model-based estimates.

Specifications of the model are detailed in appendix, as well as the results of a simulation study evaluating the operating characteristics of the proposed design.

PHASE II

The phase II is based on a one-stage design based on an efficacy endpoint (3-year bRFS). Assuming that information will be available for all patients at 3 years, the endpoint follows a binomial distribution. The design was thus defined considering exact tests, as published by A'Hern [39].

From the literature, the expected bRFS rate at 3 years is approximately 50% in this patient population with various salvage therapies. A 3-year bRFS equal to or lower than 0.50 is deemed insufficient for further evaluation of this approach [p0=0.50]. The considered alternative hypothesis is p1=0.70].

The Phase II part of the study will need to include 44 patients (including the patients recruited in the dose-finding part of the phase I, allocated at the dose level finally identified as the recommended dose). If all 44 patients are evaluable at 3 years, the treatment strategy will be considered to be insufficiently effective if ≤ 27 patients are alive without a biochemical relapse at 3 years.

The operating characteristics of the design are:

- p0=0.50, p1=0.70
- Defined Type I error = 0.05 (computed type-I error of the design = 0.048)
- Defined Power = 0.85 (computed power = 0.861)

If some patient data are censored before 3 years, the 3-year bRFS will be estimated using Kaplan-Meier method and the lower boundary of the 90% confidence interval will be compared to p0=0.50. The conclusion will be positive if we can reject the null hypothesis p0=0.50 at a one-sided 5% alpha level.

PATIENT AND PUBLIC INVOLVEMENT

Patients were not involved in the idea conception of this trial.

Patients were not involved in the design of this study nor in recruitment of the study.

Ethics and Dissemination

The study has been submitted and approved by ethics committee “Ile de France III” (2017-A00008-45) for all study sites. A written informed consent will be obtained from the study participants. In France, according to the current law, a protocol can be subjected to any regional Ethics Committee, even if no hospital of this region takes part to the trial. The choice is made according to the workload of every committee. The opinion of this Ethics Committee applies to all the national centers. Academic dissemination will occur through publication and conference presentations.

Discussion

To date, no standard local treatment exists for patients with an intraprostatic recurrence after radiotherapy. A number of treatments options exist including: radical prostatectomy, brachytherapy, HIFU, cryotherapy, and more recently SBRT. These treatments are associated with a variety of genitourinary and gastrointestinal toxicities and complications. The literature to date consists mainly of retrospective and small prospective series making it difficult to assess and compare these techniques. Philippou et al compared oncologic and toxicity outcomes of SRP versus nonsurgical therapies except SBRT with a meta-regression analysis. Oncologic and toxicity outcomes appear to be similar; however, all nonsurgical salvage modalities may be associated with better continence outcomes [40].

The sensitivity of PSMA-PET is higher than that of choline-PET for the detection of lymph node disease [41]. Unfortunately PSMA PET is not routinely available in France. A modification of the inclusion criteria is being drafted to allow PSMA PET if this examination becomes available during the study period. To have a high sensitivity, a surgical lymph node staging must be extensive, which can have side effects in this context. Furthermore clinical and biological selection criteria (no high risk cancer before first treatment, PSA level, PSA doubling time,...) are designed to select the patients to have most likely intra-prostatic recurrence only.

The phase I part of GETUG-AFU 31 trial will evaluate SBRT dose of 30 Gy in 5 fractions, over 12 days, and then depending on tolerance, 36 Gy in 6 fractions over 12 days. The latter, 36 Gy in 6 fractions, is the current scheme used at the Oscar Lambret Centre for all repeat SBRT. This dose is higher than that described by Jereczek-Fossa et al. (30 Gy in 5 fractions) [29], discussed as being too low [30], but lower than the dose used by Fuller (38 Gy in 4 fractions) [30]. A lower dose (5 x 5 Gy) was used in Zerini et al [32]. We have decided to initially use a phase I study, using dose-limiting toxicity criteria, to establish the best dose (either 5 x 6 Gy, 6 x 6 Gy, or 5 X 5 Gy) for the phase II part of the study. In phase I radiotherapy trials, late complications are often not taken into account and there is currently no consensus on the methodology used for these studies. Although most phase I radiotherapy studies use

a 3+3 design, it is not suitable for these studies as it does not assess late toxicity. More complex designs such as the TITE-CRM are recommended, which will shorten the duration of the entire trial and efficiently uses patient information throughout the study [42].

Abbreviations

GETUG-AFU: “Groupe d’Etude des Tumeurs Uro Genitales- Association Française d’Urologie”; PSA: prostate-specific antigen; RP: radical prostatectomy; EBRT: external-beam radiotherapy; SBRT: stereotactic body radiation therapy; HIFU: high-intensity focused ultrasound; bRFS: biochemical relapse–free survival; HDR: high dose rate; RTOG: radiation therapy oncology group; ADT: androgen-deprivation therapy; CTCAE: common toxicity criteria adverse events; Gy: Gray; TITE-CRM: Time-to-Event Continual Reassessment Method; IIEF: International Index of Erectile Function; CTV: clinical target volume; PTV: planning target volume; QOL: Quality of life; RTOG: Radiation Therapy Oncology Group; TUDD: time until definitive deterioration; ERG: Erythroblast transformation-specific related gene; IHC: immunohistochemistry; ARV7: Androgen-receptor splice variant 7; MRI: magnetic resonance imaging; TURP: transurethral resection of the prostate; CT: computed tomography; mpMRI: multiparametric MRI; PET: positron emission tomography; WHO: world health organization; GTV: gross tumor volume; DLT: dose limiting toxicity

Declarations

Availability of data and material

The data set used and/or analysed during the current study are available from the corresponding author on reasonable request. Not all data are obtained yet since the study is still ongoing.

Competing interests

None declared.

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Author contributions

Study Conception: DP. Revision of study design and protocol: DP, MCLD, ET, LC, MD, SN, ERL. Study coordination: DP, MCLD, ET, SN. All authors read and approved the final manuscript.

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None

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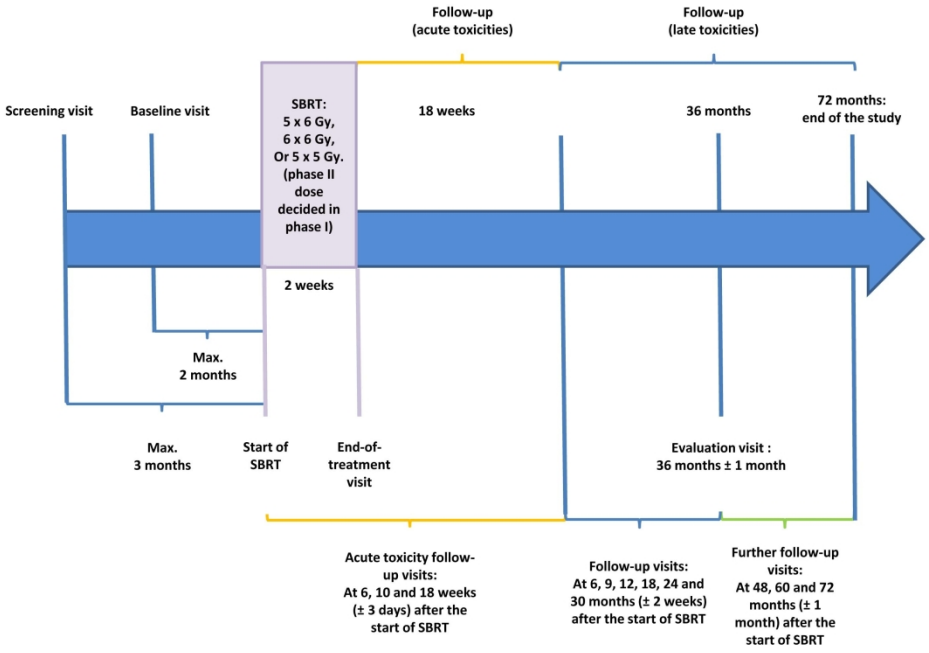
Figures legends

Fig. 1 Overview of study flow chart. SBRT: stereotactic body radiotherapy

Fig 2. Detailed description of study flow chart.

(1.Patient will be contacted by phone 14 weeks after starting SBRT to assess toxicity; an additional visit may be scheduled if required; 2 .Before inclusion, during regular follow-up and in case of biochemical recurrence after SBRT; 3 .Before inclusion and in case of biochemical recurrence after SBRT; 4.Patient's height will only be measured at the screening visit; 5. If not done at the screening visit.; 6.Only applicable for patients who have consented to participate in the biological ancillary study)



254x190mm (300 x 300 DPI)

	Screening	Baseline		End of RT visit (at last RT session)	Acute toxicity follow-up visits 6, 10, and 18 weeks (±3 days) after starting SBRT				Follow-up visits 6, 9, 12, 18, 24, and 30 (±2 weeks) after starting SBRT						Evaluation visit 36 months (±1 month) after starting SBRT	Further follow-up visits 48, 60 and 72 months (±1 month) after starting SBRT/End of Study		
Visits	**ScV**	**BV**		**End RT**	**W6**	**W10**	**W14**[1]	**W18**	**M6**	**M9**	**M12**	**M18**	**M24**	**M30**	**M36**	**M48**	**M60**	**M72/End of Study**
Eligibility criteria	X	X																
Signed informed consent form	X																	
Enrollment in the study		X																
CLINICAL EXAMINATION																		
Weight, height[4] PS (WHO)	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X
Digital rectal examination (clinical stage)	X	X[5]							X		X	X	X	X	X	X	X	X
Uroflowmetry		X																
Medical history of prostate cancer		X																
Grading of functional digestive, urinary and sexual symptoms (NCI-CTCAE V4.03)		X		X	X	X		X	X	X	X	X	X	X	X	X	X	X
QUESTIONNAIRES																		
QLQ-C30 and QLQ-PR25		X							X		X	X	X	X	X	X	X	X
IPSS		X						X	X		X	X	X	X	X	X	X	X
IIEF5		X						X	X		X	X	X	X	X	X	X	X
LABORATORY TESTS																		
CBC, platelets		X																
PT, PTT, and INR		X																
PSA		X						X		X	X	X	X	X	X	X	X	X
PATHOLOGICAL EVALUATION																		
Gleason score; number of positive biopsies, total number of biopsies; total length of cancer on biopsies; total length of biopsies	X																	
PARACLINICAL INVESTIGATION																		
Multi-parametric MRI (pelvic and prostate)	X[2]								X		X		X		X	X	X	X
Choline PET scan	X[3]																	
TNM evaluation	X																	
TRANSLATIONAL RESEARCH																		
Prostrate tumor biopsies (Initial before any treatment and at recurrence before SBRT)		X[6]																

Fiducial placement and treatment planning followed by SALVAGE-SBRT

1.Patient will be contacted by phone 14 weeks after starting SBRT to assess toxicity; an additional visit may be scheduled if required; 2 .Before inclusion, during regular follow-up and in case of biochemical recurrence after SBRT; 3 .Before inclusion and in case of biochemical recurrence after SBRT; 4.Patient's height will only be measured at the screening visit; 5. If not done at the screening visit.; 6.Only applicable for patients who have consented to participate in the biological ancillary study (see section 8.)

263x162mm (300 x 300 DPI)

GETUG-AFU 31: a phase I/II multi-center study evaluating the efficacy of repeat stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation therapy.

Appendix: statistical model, simulation study

Statistical considerations

A TITE-CRM method with an empiric dose-toxicity model in a Bayesian framework will be used for the dose-finding part of the trial to identify the recommended dose. The target dose-limiting toxicity (DLT) probability is set at p(DLT)=0.25. Three dose levels of SBRT are to be considered: 5 x 5 Gy (DL-1), 5 x 6 Gy (DL1), 6 x 6 Gy (DL2). The starting dose level is 5 x 6 Gy and dose level 5 x 5 Gy will be explored in case of DLT at the starting dose level. DLTs are evaluated during the 18 weeks following the initiation of salvage-SBRT. Observations of patients who have no DLT at the time of the analysis but have not completed the DLT assessment period will be down-weighted in the likelihood, proportionally to the length of follow up.

The Phase I part of the study will include 3 patients at the first dose level. Radiation dose levels for further patients will be defined based on the estimate of the probability of DLT at each dose-level considering all available information accumulated so far. Patients will be treated at the best current estimate of the recommended dose i.e. the dose associated with an estimated probability of DLT the closest to the target 0.25. Patients may eventually be treated at a dose below the dose recommended by the model for safety reasons. The patients can be recruited with no minimal time interval between successive inclusions. Two additional rules will be applied during dose escalation: no dose skipping and no escalation if at least 1 DLT is observed in the last 3 patients.
The dose-escalation part of the study will terminate once 10 patients have been treated and evaluated at a dose currently identified as the recommended dose. Further patients will then be accrued in the expansion cohort, where toxicity data collected over the first 18-week period and DLT assessment will be analyzed approximately every 10 patients with the possibility of modification of the recommended dose, based on model-based estimates.
The Phase II part of the study will need to include 44 patients, including the patients recruited in the dose-finding part of the phase I allocated at the dose level finally identified as the recommended dose. Thus, a minimal sample size of 47 patients will be required in this Phase I/II study (in the case of inclusion of 44 patients at dose level 2 + 3 patients at dose level 1).

Statistical model for dose escalation

A one-parameter empirical power model will be used to assess the relation between the dose level and the probability of DLT: $F(d,\alpha) = p_d^{\exp(\alpha)}$ where $F(d,\alpha)$ is the estimated probability of DLT at dose-level d, p_d is the prior probability of DLT at dose level d, and α is the unknown parameter to be estimated by the model. The vector $\{p_{0d}\}$ represent the initial guesses of toxicity probabilities, reflecting the clinicians' prior belief. The skeleton of initial guesses of toxicity probabilities $\{p_{0d}\}$ is numerically calibrated using the Lee and Cheung approach (ref ClinTrials 2009) and using the getprior function of R, ensuring good design's operating characteristics. After discussion with the clinicians, the delta defining the indifference interval was set at 0.05 (p(DLT)=0.25 +/- 0.05, i.e. indifference interval: 0.20 to 0.30) and the prior MTD (MTD_0) at the 2nd dose level, meaning that the clinicians believe, a priori, that the 2nd dose (6 x 6 Gy) is probably the MTD. This yields a vector of prior probabilities $\{p_{0k}\}$ equal to 0.08, 0.16 and 0.25 for dose level -1 (5 x 5Gy), dose level 1 (5 x 6 Gy) and dose level 2 (6 x 6 Gy). The clinicians confirmed that it was in accordance with their initial guesses. A non-informative prior distribution Normal (0, 1.34) has been assigned for α in the Bayesian

computation. The simulation study below confirmed that the operating characteristics and the behavior of the model defined with these parameters were reasonable.

Operating characteristics:

The operating characteristics of the proposed design were evaluated using the R titesim function written by Cheung, and considering six different scenarios:

- highly toxic,
- moderately toxic at dose levels -1 and 1, highly toxic at dose level 2
- moderately toxic et every dose level,
- similar with prior probabilities,
- close to the probabilities but a little less toxic,
- little toxic

For the simulation study, we considered that the trial would recruit 47 patients, which is the minimal sample size required in this Phase I/II study.
The following rules were implemented: no dose skipping in escalation, and no escalation if >1 DLT observed among < 3 patients.
For each case, 1000 trials were simulated. The Monte Carlo estimation of the percentage of dose selection, the average number of patients treated at each dose level, the average number of observed DLTs at each dose level demonstrated that the modified CRM design can efficiently identify the MTD, with a reasonable probability of overdosing, and expose few patients to toxicity.
A second set of simulations was performed considering a sample size of 13 patients, which is the minimal expected recruitment in the Phase I part of the study. As expected, the performance is much better when the reassessment is continued during the expansion phase (Phase II part). This is one of the advantages of the CRM method.

Figure 1: Scenarios studied

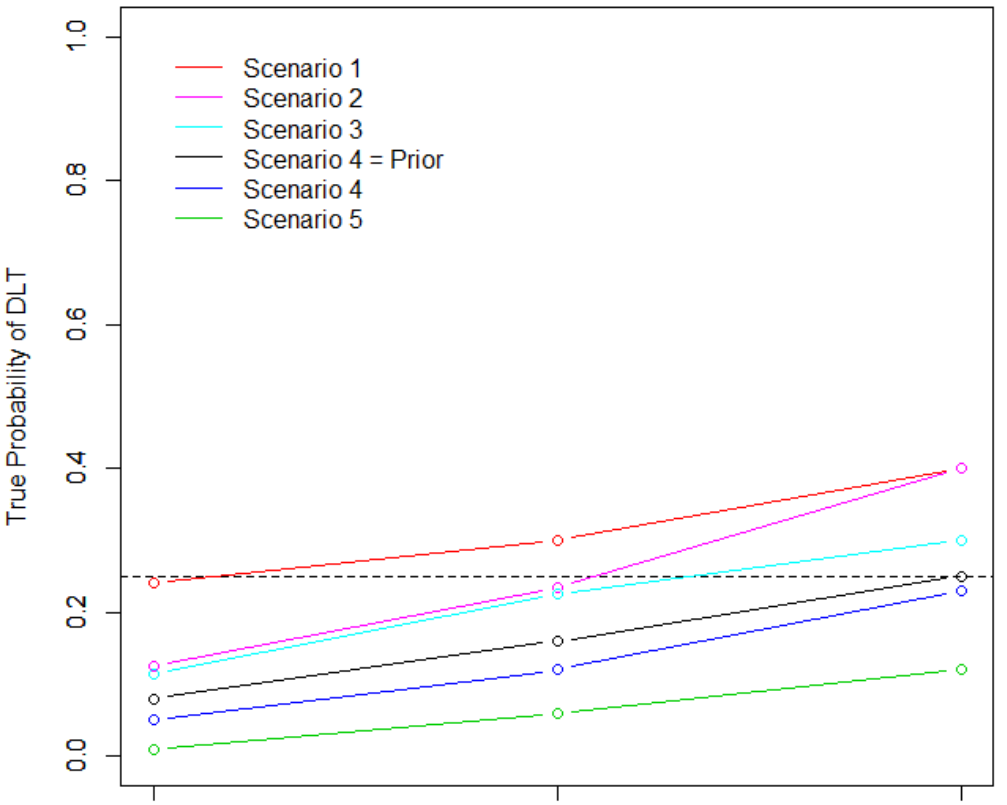


Table 1 : Operating characteristics for five different scenarios for the probability of DLT per dose

1a – Simulation for a recruitment of 47 patients (minimal sample size required in this Phase I/II study)

The grey row represents the true MTD (proba(DLT) closest to the target of 0.25.

SCENARIO 1 : highly toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.24	0.57	23.7	5.7	0.12
1 (5 x 6 Gy)	0.30	0.37	13.4	4.0	0.085
2 (6 x 6 Gy)	0.40	0.06	9.9	4.0	0.085

Expected number of DLTs over the whole trial (47 patients) = 13.7 / trial; 29% patients

SCENARIO 2: moderately toxic at dose levels -1 and 1, highly toxic at dose level 2

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.12	0.12	10.9	1.3	0.03
1 (5 x 6 Gy)	0.23	0.69	21.7	5.1	0.11
2 (6 x 6 Gy)	0.40	0.19	14.4	5.8	0.12

Expected number of DLTs over the whole trial (47 patients) = 12.1 / trial; 26% patients

SCENARIO 3: moderately toxic at every dose level

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.12	0.08	8.0	1.0	0.02
1 (5 x 6 Gy)	0.23	0.52	17.0	3.9	0.08
2 (6 x 6 Gy)	0.30	0.40	22.0	6.7	0.14

Expected number of DLTs over the whole trial (47 patients) = 11.6 / trial; 24% patients

SCENARIO 4 : true proba(DLT) = prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.08	0.006	3.2	0.3	0.01
1 (5 x 6 Gy)	0.16	0.22	11.3	1.8	0.04
2 (6 x 6 Gy)	0.25	0.78	32.5	8.2	0.17

Expected number of DLTs over the whole trial (47 patients) = 10.3 / trial; 22% patients

SCENARIO 5: little less toxic than prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.05	0.001	2.2	0.1	0.002
1 (5 x 6 Gy)	0.12	0.09	8.4	1.0	0.02
2 (6 x 6 Gy)	0.23	0.91	36.4	8.4	0.18

Expected number of DLTs over the whole trial (47 patients) = 9.5 / trial; 20% patients

SCENARIO 6: little toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.01	0	0.8	0.003	<0.001
1 (5 x 6 Gy)	0.06	0	2.3	0.1	0.002
2 (6 x 6 Gy)	0.12	1.0	43.9	5.3	0.113

Expected number of DLTs over the whole trial (47 patients) = 5.4 / trial; 11.5% patients

*% of DLT: mean n. of DLT / total number of patients

1b – Simulation for a recruitment of 13 patients (minimal sample size required in the Phase I part of the study)

The grey row represents the true MTD (proba(DLT) closest to the target of 0.25.

SCENARIO 1 : highly toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.24	0.52	4.7	1.1	0.08
1 (5 x 6 Gy)	0.30	0.27	2.7	0.8	0.06
2 (6 x 6 Gy)	0.40	0.21	5.6	2.2	0.17

Expected number of DLTs over the whole trial (13 patients) = 4.1 / trial; 31% patients

SCENARIO 2: moderately toxic at dose levels -1 and 1, highly toxic at dose level 2

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.12	0.30	3.8	0.5	0.04
1 (5 x 6 Gy)	0.23	0.39	3.2	0.7	0.05
2 (6 x 6 Gy)	0.40	0.31	6.0	2.4	0.19

Expected number of DLTs over the whole trial (13 patients) = 3.6 / trial; 28% patients

SCENARIO 3: moderately toxic at every dose level

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.12	0.21	3.0	0.4	0.03
1 (5 x 6 Gy)	0.23	0.33	3.0	0.7	0.05
2 (6 x 6 Gy)	0.30	0.46	7.0	2.1	0.17

Expected number of DLTs over the whole trial (13 patients) = 3.2 / trial; 25% patients

SCENARIO 4 : true proba(DLT) = prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.08	0.09	2.1	0.2	0.02
1 (5 x 6 Gy)	0.16	0.27	2.8	0.5	0.04
2 (6 x 6 Gy)	0.25	0.64	8.0	2.0	0.15

Expected number of DLTs over the whole trial (13 patients) = 2.7 / trial; 21% patients

SCENARIO 5: little less toxic than prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.05	0.05	1.6	0.1	0.01
1 (5 x 6 Gy)	0.12	0.21	2.7	0.3	0.02
2 (6 x 6 Gy)	0.23	0.74	8.7	2.0	0.15

Expected number of DLTs over the whole trial (13 patients) = 2.4 / trial; 18% patients

SCENARIO 6: little toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.01	0.004	0.6	0.01	0.001
1 (5 x 6 Gy)	0.06	0.04	1.8	0.09	0.007
2 (6 x 6 Gy)	0.12	0.96	10.6	1.3	0.10

Expected number of DLTs over the whole trial (13 patients) = 1.4 / trial; 11% patients

*% of DLT: mean n. of DLT / total number of patients

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	ItemNo	Description	Protocol Page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Phase I/II Multi-center Study Evaluating the Efficacy of Repeat Stereotactic Radiation in Patients With Intraprostatic Tumor Recurrence After External Radiation Therapy (STEREO-RE-PRO)	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ClinicalTrials : NCT03438552	2
	2b	All items from the World Health Organization Trial Registration Data Set IdRCB : 2017-A00008-45	2
Protocol version	3	Date and version identifier version n°2.0 06/10/2017	1
Funding	4	Sources and types of financial material, and other support Support by a grant of National Institute of Cancer (INCA)	Not explicitly mentioned in the protocol
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Docteur David PASQUIER Centre Oscar Lambret - Département de Radiothérapie 3, rue Fréderic Combemale - BP307 59020 Lille Cedex Tél : 03.20.29.59.11 - Fax : 03.20.29.58.96 E-mail : d-pasquier@o-lambret.fr	2

	5b	Name and contact information for the trial sponsor **UNICANCER** 101 Rue de Tolbiac, 75654 Paris Soazig NENAN +33 (0)185 343 113 s-nenan@unicancer.fr Meryem BRIHOUM +33 (0)1 80 50 12 95 m-brihoum@unicancer.fr	1-2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	46; 49
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	42-44; 46
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	17-22
	6b	Explanation for choice of comparators	Not applicable

Objectives	7	Specific objectives or hypotheses **Primary objective** : Selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity observed during the 18 weeks following the initiation of salvage-SBRT. Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate **Secondary objectives** Evaluation of acute and late genitourinary toxicities of the salvage-SBRT Estimate the efficacy of the salvage-SBRT in terms of clinical progression-free survival and overall survival Evaluation of Quality of life after salvage-SBRT	22-23
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Study Type: Interventional Primary Purpose: Treatment Intervention Model: Sequential Assignment Number of Arms: 3 Masking: Open Label Endpoint Classification: Safety/Efficacy Study Enrollment: 47	4

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Centers are hospitals and clinics (see below) : Centre François Baclesse, Caen, France Principal Investigator: Marlon SILVA Centre Jean Perrin, Clermont-Ferrand, France Principal Investigator: Geneviève LOOS Centre George François Leclerc, Dijon, France Principal Investigator: Gilles CREHANGE Centre Oscar Lambret, Lille, France Principal Investigator: David PASQUIER Centre Léon Bérard, Lyon, France Principal Investigator: Pascal Pommier Institut régional du Cancer de Montpellier, Montpellier, France Principal Investigator: David AZRIA Groupe Hospitalier Pitié-Salpétrière, Paris, France Principal Investigator: Philippe MAINGON ICO -Site René Gauducheau, Saint-Herblain, France Principal Investigator: Stephane SUPIOT Institut de Cancérologie Lucien Neuwirth, Saint-Priest-en-Jarez, France Principal Investigator: Nicolas MAGNE	Additional form (not in the protocol)

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	26-27

Minimum Age: 18 Years
Gender: Male
Accepts Healthy Volunteers?: No

Inclusion Criteria:

1. Biochemical recurrence occurring at least 2 years after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL)
2. T1-T2c and PSA ≤20 ng/mL and Gleason score ≤7 at initial diagnosis of prostate cancer before the initial/first treatment.
3. Recurrence of prostatic adenocarcinoma proven by histology following radiotherapy by transrectal or transperineal sextant biopsies of the two lobes of the prostate, with a minimum of 12 biopsies, irrespective of Gleason score. Biopsies of the seminal vesicles are optional.
4. Clinical stage T1-T2 on relapse; unilateral extracapsular extension (T3a) on MRI permitted except posteriorly relative to the rectum
5. Estimated clinical target volume (CTV) / prostate volume < 0.5 based on imaging and biopsies
6. Pelvic and prostatic assessment by multiparametric MRI-Absence of pelvic or metastatic recurrence proven by choline PET scan
7. Performance status WHO 0-1
8. PSA level ≤10 ng/mL at baseline (before salvage-SBRT)
9. PSA doubling time >10 months
10. International Prostate Cancer Score (IPSS) ≤12
11. Uroflowmetry with a maximum flow rate >10 mL/s, a postvoid residual urine volume <150 mL, and a urine volume >150 mL.
12. No other anti-cancer treatment since the external radiotherapy administered as first-line treatment
13. No other anti-cancer treatment planned for the current recurrence
14. No contraindication to fiducial marker implants; haemostatic disorders must be corrected before implantation
15. Age >18 years
16. Life-expectancy greater than or equal to 5 years (Lee scale)
17. Patient registered with a health insurance system
18. Patient who has signed the informed consent form
19. Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests, and other study procedures indicated in the protocol.

Exclusion Criteria:

1. Lymph node or metastatic spread
2. Late post-radiotherapy urinary or gastrointestinal toxicity of grade ≥2 (following primary radiotherapy)
3. Other cancers in the last 5 years except for non-melanoma-type skin cancer
4. History of inflammatory bowel disease
5. Anticoagulant treatment
6. Contraindications to undergoing MRI
7. Prostate volume >80 cc
8. Transurethral resection of the prostate (TURP) in the 6 months before registrations
9. Presence of rectal telangiectasia grade 3 classified by the Vienne Rectoscopy Score (obligatory rectoscopy)
10. Previous rectal surgery
11. Patients unable to undergo medical follow-up in the study for geographical, social or psychological
12. Person deprived of their liberty or under protective custody or guardianship
13. Patients enrolled in another therapeutic study

All patients during the SBRT planning with a ratio of clinical target volume (CTV) / prostate volume > 0.5 will be withdrawn from the study. These patients will be considered as not evaluable and will

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	28-30
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) Not applicable	31
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Not applicable	31
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Concomitant treatment permitted : any treatment considered necessary for the health of the patient	31
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Primary Outcome Measure:** [Time Frame: 18 weeks] Selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity observed during the 18 weeks following the initiation of salvage-SBRT. The dose-escalation part of the study will terminate once 10 patients have been treated and evaluated at a dose currently identified as the recommended dose. [Time Frame: 6 years] Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate **Secondary Outcome Measure:** 1. Time Frame: 3 years] Evaluation of acute and late genitourinary toxicities of the salvage-SBRT 2. [Time Frame: 6 years] Estimate the efficacy of the salvage-SBRT in terms of clinical progression-free survival and overall survival 3. [Time Frame: 6 years] Evaluation of Quality of life after salvage-SBRT	23-24

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	24-25; 31-35
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations At least 47 patients **Sample Size Calculations**	39-40
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Communication and follow-up of the participating centers	44; 50
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions TITE-CRM	25; 39-40
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned Number of inclusion attributed directly by eCRF	25
Implementation	16c	Who will generate the allocation sequence: computer/eCRF by inclusion program. Biostatistician who will enrol participants: Investigator. and who will assign participants to interventions: Biostatistician.	25
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how Not applicable	Not applicable

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Not applicable	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Describe in protocol and data management procedures	30; 31-35; 43-44
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols Describe in protocol and data management procedures	31; 31-35
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Describe in protocol and data management procedures	30; 43-44
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	41-42
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) Not applicable	41-42
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Not applicable	41-42
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Coordinator : validate the risk analysis (LIR) and the monitoring plan Project Manager : determine the risk analysis (LIR) and write the monitoring plan Clinical Research Associate (CRA) :perform monitoring according the monitoring plan	42
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	42
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct This point is provided by the vigilance unit of the sponsor. All details are described in the protocol	35-38
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Actually and according the risk analysis, no audit is planned	44
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval N° IdRCB : 2017-A00008-45 Initial Approval by CPP Nord-Ouest I (Committee for the Protection of Personnes/Ethic committee) : 25/07/2017 Approval Number: CPP3517-I	45

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) Each major protocol amendment is submitted to authorities for approval. After approval, it is communicated to all the actors of this project (investigators, trial centers, trial registry ….)	46
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Principal Investigator or sub-investigator	47
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Not applicable	33; 38; 48
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Collected by investigators and CRA on each trial centers. These data are anonymized. Shared on the eCRF. There is a control access on the eCRF	43; 47-49
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site None	Not applicable
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Directly on the eCRF	48-49
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation Not applicable	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions A publication is planned; no publication restriction.	50

	31b	Authorship eligibility guidelines and any intended use of professional writers Coordinator will be the first author; co investigators will be authors.	50
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code N/A	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional form (not in the protocol)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable Not applicable	59

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.