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# BMJ Open

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

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3 GETUG-AFU 31: a phase I/II multi-center study evaluating the efficacy of salvage  
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5 stereotactic radiation in patients with intraprostatic tumor recurrence after external  
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7 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. Stereotactic 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  $\geq 3$  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

Date of trial registration: November 14, 2017

**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

peer review only

## 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  $\geq 81$  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  $\leq 6$  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  $\geq 2$  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

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

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7 Salvage RP is a treatment option after local recurrence following EBRT. However, the morbidity,  
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9 including incontinence and erectile dysfunction, is higher than that observed with first-line RP  
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11 patients. A systematic literature review [7] reported that the probability of biochemical relapse-free  
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13 survival (bRFS) following salvage-RP in prostate cancer patients was 47-82% after 5 years and 28-53%  
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15 after 10 years. At 10 years, cancer-specific survival ranged from 70% to 83% and overall survival from  
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17 54% to 89%. The preoperative PSA level and prostate-biopsy Gleason score were the strongest  
18  
19 prognostic risk factors for PFS and cancer-specific survival. Salvage-RP after radiotherapy compared  
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21 to primary RP has a significantly higher rate of urinary and gastrointestinal morbidity.[8] The review  
22  
23 above [7], reported that the most frequent complications were anastomotic stricture (7-41%) and  
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25 rectal injury (0-28%). The majority (50-91%) of men had erectile dysfunction before salvage-RP and  
26  
27 80-100% after surgery. Post-operative urinary continence ranged from 21-90%.

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30 In a recent review, salvage brachytherapy (BT) after EBRT is reported to achieve biochemical  
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32 control rates of 20% to 89% (median follow-up: 19 to 108 months).[9] Rates of genitourinary  
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34 toxicities range from 12% to 87% for grade 1-2, and 3% to 47% for grade 3-4 toxicities. Similarly, the  
35  
36 rates of gastrointestinal toxicities range from 4% to 65% for grade 1-2, and 0% to 20% for grade 3-4  
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38 toxicities. Erectile dysfunction was observed in 2% to 95% of men. A phase II study of salvage high-  
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40 dose-rate (HDR) BT for treating recurrent prostate cancer after definitive external beam radiotherapy  
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42 was reported by Yamada.[10] The 42 patients enrolled, with biopsy proven recurrence, were treated  
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44 with salvage HDR (iridium-192) with a resulting bRFS at 5 years of 68.5% (median follow-up of 36  
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46 months [range: 2-66 months]). Acute genitourinary toxicity was observed: grade 1, 38% of patients  
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48 and grade 2, 40%. Similarly, late genitourinary toxicity was observed: grade 1, 38% of patients and  
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50 grade 2, 48%. In addition, 1 patient had a grade 3 urinary incontinence and 3 had grade 3 urethral  
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52 strictures. Late gastrointestinal toxicities were observed: grade 1, 43% of patients and grade 2, 14%.  
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54 More recently, a study of 83 prostate cancer patients with local recurrence after radiotherapy  
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2 treated with HDR BT was reported.[11] The median follow-up was 41 months. The 3-year and 5-year  
3 bRFS were 76% and 67%. A phase II study of the RTOG in 100 patients was recently presented: twelve  
4 (14%) experienced late grade 3 genitourinary/gastrointestinal adverse effects. This rate of late grade  
5 3 toxicity (14%) was not unacceptable by the predetermined protocol specification, without any  
6 grade 4-5 events. The only factor predictive of late toxicity was implant dose, underlining the need  
7 for meticulous planning and technique to limit the final delivered dose.[12] In France, a phase II  
8 study, “Brachytherapy for Recurrent Prostate Cancer” (CAPRICUR) was recently completed.[13]

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17 HIFU is another less invasive salvage treatments following recurrence.[14] A French group treated  
18 290 men with biopsy-confirmed recurrent prostate cancer.[15] The mean follow-up was 48 months  
19 after HIFU. At 7 years, the cancer-specific survival rate was 80% and the metastasis-free survival rate  
20 was 79.6%. Recto-urethral fistula occurred in 0.4% of patients and 19.5% had grade 2/3 incontinence.  
21 Half of the patients also received androgen deprivation therapy (ADT). Survival without relapse at 5  
22 years after HIFU, by D’Amico risk groups prior to their initial treatment, was 45% (favorable), 31%  
23 (intermediate risk) and 21% (high risk). In this cohort, the grade  $\leq 3$  urinary incontinence levels were  
24 23% (favorable), 14% (intermediate risk) and 9% (high risk). Nearly 8% of patients required an  
25 artificial sphincter following HIFU. Importantly, pubic osteitis occurred in 2.5% of patients despite  
26 adherence to parameters specific to HIFU following radiotherapy.[15]

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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-

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3 92); the 5-year bRFS rate (Phoenix definition) was 43.5% and with a 5-year overall survival rate of  
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5 92.3%. Mild complications (grades 1 and 2) were reported including: mild incontinence (9.4%), acute  
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7 rectal pain (31.3%), haematuria (6.3%), scrotal oedema (9.4%), urinary tract infection (3.1%), lower  
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9 urinary tract symptoms (15.6%) and erectile dysfunction (57.1%). Grade 3 toxicities: incontinence  
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11 (3.1%) and urethral sloughing (3.1%) were observed.

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13 ADT alone (continuous or intermittent) is commonly given to patients with biochemical relapse  
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15 after radiotherapy.[20] In a series based on data from a North American national registry (CaPSURE),  
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17 71% of patients were treated for biochemical relapse after prostatectomy or radiotherapy. ADT was  
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19 initiated in 93% of these patients, and the remaining patients were treated with surgery,  
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21 brachytherapy, cryotherapy, or repeat external radiotherapy.[21] ADT may cause adverse effects  
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23 impacting patient's quality of life (including: hot flushes, erectile dysfunction and reduced libido,  
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25 cognitive impairment, and anemia). The metabolic changes associated with hormone therapy may  
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27 also increase the risk of cardiovascular morbidity. The reduction in bone mass is maximal in the first  
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29 year and increases with the duration of castration; the risk of fracture is increased in patients  
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31 surviving for more than 5 years.[22-23] The guidelines suggest that a simple follow-up can be  
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33 implemented for local recurrence in patients with a limited life expectancy or for those who do not  
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35 wish to undergo local salvage treatment. The European Association of Urology guidelines [24]  
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37 recommended to perform salvage surgery in experienced centres due to the increased rate of side  
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39 effects. It is recommended to offer/discuss HIFU, cryosurgical ablation and salvage brachytherapy  
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41 to/with patients without evidence of metastasis and with histologically proven local recurrence and  
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43 to inform patients about the experimental nature of these approaches. The level of evidence for each  
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45 of these recommendations is 3.[24]

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49 SBRT delivers highly conformal, high-dose radiation in a few fractions (hypofractionation), typically  
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51 5 to 7 fractions for prostate cancer. It is reported that tissues with a low  $\alpha/\beta$  ratio, as for prostate  
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53 cancer, are more sensitive to large doses of radiation per fraction. This suggests that  
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55 hypofractionation may result in improved tumor control with limited toxicity. A pooled analysis of  
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3 1100 patients included in separate prospective phase II studies was performed to evaluate the  
4 effectiveness of SBRT as a first-line treatment for localized prostate cancer.[25] The SBRT was  
5 delivered by CyberKnife with a median dose of 36.25 Gy in 4-5 fractions. The 5-year bRFS rate was  
6 93% for all patients. Thus relapse-free survival rates after SBRT compare favourably with other  
7 definitive treatments for low and intermediate-risk patients with a short follow up. SBRT is well  
8 tolerated with a low effect on quality of life.[25-28] In addition sexual function appeared to be  
9 spared in the majority of patients.[25-28]

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17 SBRT has also been used as a salvage treatment following failure of external radiotherapy.  
18 Jereczek-Fossa et al. published data on 34 consecutive patients treated with robotic SBRT for isolated  
19 recurrent primary, lymph node, or metastatic prostate cancer.[29] Of the 34 patients, 15 patients  
20 had intraprostatic recurrence, confirmed by biopsy, and were treated with SBRT (CyberKnife) with a  
21 median dose of 30 Gy in 5 fractions. The median survival without recurrence was 13 months. Urinary  
22 toxicity was low, with a grade 3 urinary toxicity in only one patient. No case of acute or late  
23 gastrointestinal toxicity was reported. This good gastrointestinal tolerability has subsequently been  
24 confirmed.[29-32] In Fuller et al twenty-nine patients were treated in a phase II trial with SBRT for  
25 intraprostatic recurrence.[30] Eligible patients had to present biopsy-proven intraprostatic  
26 recurrence graded T1 to T3N0M0 more than 2 years post-radiotherapy and without a pre-existing  
27 grade >1 radiotherapy toxicity. The prior median dose delivered was 73.8 Gy and the median interval  
28 between the treatments was 88 months. The dose delivered to the entire gland was 34 Gy in five  
29 fractions over 5 days. With a median follow-up of 24 months, survival without recurrence was 82%.  
30 Toxicity was acceptable, with 18% grade  $\geq 2$  urinary toxicity, including one patient with a grade 4  
31 toxicity, and no late gastrointestinal toxicity above grade 1. Particular attention should be given to  
32 patients who still exhibit urinary toxicity after initial radiotherapy.[30] Our preliminary retrospective  
33 results in 23 patients treated for this indication were published recently.[31] A total dose of 36 Gy  
34 was prescribed in 6 fractions of 6 Gy. Nineteen patients had a whole-gland and four a partial  
35 treatment. Median follow-up was 23 months (range 6 to 40 months). We observed no grade 4 or 5  
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3 toxicity. Two patients presented grade 3 toxicities. Others toxicities include urinary (5 grade 2 and 9  
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5 grade 1) and rectal toxicities (2 grade 2 and 2 grade 1).  
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7 To date, no standard local treatment exists for patients with an intraprostatic recurrence after  
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9 radiotherapy.[33] A number of treatments options exist including: radical prostatectomy,  
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11 brachytherapy, HIFU, cryotherapy, and stereotactic radiotherapy. The literature to date consists  
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13 mainly of retrospective and small prospective series making it difficult to assess and compare these  
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15 techniques. In recent years, SBRT has been used to treat localized prostate cancer in the primary  
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17 setting but also as a salvage treatment after failure of radiotherapy. The initial results of these  
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19 retrospective studies are promising, with respect to survival and tolerance, but further studies are  
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21 required to confirm these initial results. Our proposed study will provide further evidence of SBRT as  
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23 a supplementary non-invasive curative treatment for local recurrence following radiotherapy. This  
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25 study could provide the foundation for prospective studies comparing the available salvage  
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27 treatments after radiotherapy.  
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## 32 **METHODS AND ANALYSIS**

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34 This study is approved by the Ethics committee "Ile de France III" (2017-A00008-45) and is registered  
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36 on [clinicaltrials.gov](http://clinicaltrials.gov) (NCT03438552). Inclusion and exclusion criteria are described in Table 1. This  
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38 multicenter open-labelled phase I/II study will initially select the SBRT scheme (phase I), either 5 x 6  
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40 Gy, 6 x 6 Gy, or 5 x 5 Gy. The effectiveness of SBRT scheme selected in phase I will then be evaluated  
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42 in a single-arm multicenter phase II study.  
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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  $\leq$ 20 ng/mL and Gleason score  $\leq$ 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  $\leq$ 10 ng/mL at baseline (before salvage-SBRT)
- o PSA doubling time  $>$ 10 months
- o IPSS  $\leq$ 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  $\geq$ 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

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

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

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16 The phase II secondary objectives are:

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○ 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.

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

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15 A flow chart presenting the different steps from inclusion until treatment is presented in Figure 1.

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17 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

18 delivered over a maximum of 12 days to provide a total dose of 25 to 36 Gy. This radiotherapy may

19 be administered with the CyberKnife® or a linear accelerator allowing stereotactic radiotherapy.

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21 An mpMRI and CT-scan will be carried out at least one week after fiducial implantation. After image

22 transfer to a planimetric console, fiducial-based registration with the prostatic mpMRI will take place

23 in order to provide a better definition of the Gross Target Volume (GTV) and prostatic contours,

24 especially the apex. Multimodality image registration with Choline PET is possible but not mandatory.

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32 Delineation of the target volume will be carried out by a radiotherapist experienced in the

33 definition of prostate volumes on CT-scans and MRIs. GTV will be represented by lesion defined on

34 the mpMRI +/- choline PET; a 5-7 mm margin around the GTV will be used to define the Clinical

35 Target Volume (CTV). CTV is contained in the prostate, except in the case of extracapsular extension

36 (unilateral extracapsular extension on MRI permitted except posteriorly relative to the rectum). In

37 the case where the positive biopsy(ies) are outside and adjacent to the visible lesions on the MRI, the

38 zone containing these biopsies must be included in the CTV so that the prostate cancer recurrence

39 not visible on the MRI is included in the CTV. The total CTV should not be more than half of the total

40 volume of the prostate by MRI. The planning target volume (PTV) will be obtained by an expansion of

41 2 mm around the CTV in this repeat radiotherapy context. This margin involves that the probability of

42 coverage at 25, 30, or 36 Gy is low, so the reporting will include D2%, 50%, D98% and D95% to

43 describe as much as possible delivered dose.

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

21 Required number of patients to be included: minimum 47 patients. The total sample size will depend  
22 upon the number of patients allocated at the different dose levels in the dose-finding parts of the  
23 trial. A total of 44 patients allocated at the recommended dose and evaluable at 3 years are required  
24 for the main analysis of the Phase II part of the trial to ensure an 85%-power if 3-year bRFS is  
25  $p_1=0.70$ , with a test against  $p_0=0.50$  at a one-sided 5%-alpha level.  
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#### 34 STATISTICAL CONSIDERATIONS

##### 35 PHASE I

36 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  
37 level is 5 x 6 Gy. A TITE-CRM with an empiric dose-toxicity model in a Bayesian framework will be  
38 used for the dose-finding part of the trial to identify the recommended dose. The target dose limiting  
39 toxicity (DLT) probability is set at  $p(\text{DLT})=0.25$ . Observations of patients who have no DLT at the time  
40 of the analysis but have not completed the DLT assessment period will be down-weighted in the  
41 likelihood, proportionally to the length of follow up; for instance, if the last patient has been  
42 recruited 8 weeks before a new patient is available for enrolment, and is evaluated at week 10 with  
43 no DLT, then his observation is attributed a weight of  $10/18=0.56$ .  
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3 At least three patients will be enrolled at the first dose-level and fully evaluated over the 18-week  
4 study period before the dose is escalated to the next dose-level. Radiation dose levels for further  
5 patients will be defined based on the estimate of the probability of DLT at each dose-level  
6 considering all available information accumulated so far. Patients will be treated at the best current  
7 estimate of the recommended dose i.e. the dose associated with an estimated probability of DLT the  
8 closest to the target 0.25. Patients may eventually be treated at a dose below the dose  
9 recommended by the model for safety reasons. The patients can be recruited with no minimal time  
10 interval between successive inclusions. During the dose-escalation part of the trial, safety data will  
11 have to be reported in the data base in real time. Safety data will be discussed with an Independent  
12 Data Monitoring Committee (IDMC) at the end of the dose-escalation part of trial, or before if  
13 needed.  
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26 The dose-escalation part of the study will terminate once 10 patients have been treated and  
27 evaluated at a dose currently identified as the recommended dose. Further patients will then be  
28 accrued in the expansion cohort, where toxicity data collected over the first 18-week period and DLT  
29 assessment will be analyzed approximately every 10 patients with the possibility of modification of  
30 the recommended dose, based on model-based estimates.  
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36 Specifications of the model are detailed in Appendix, as well as the results of a simulation study  
37 evaluating the operating characteristics of the proposed design.  
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## 43 PHASE II

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45 The phase II is based on a one-stage design based on an efficacy endpoint (3-year bRFS). Assuming  
46 that information will be available for all patients at 3 years, the endpoint follows a binomial  
47 distribution. The design was thus defined considering exact tests, as published by A'Hern.[39] From  
48 the literature, the expected bRFS rate at 3 years is approximately 50% in this patient population with  
49 various salvage therapies. A 3-year bRFS equal to or lower than 0.50 is deemed insufficient for  
50 further evaluation of this approach [ $p_0=0.50$ ]. The considered alternative hypothesis is [ $p_1=0.70$ ].  
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3 The Phase II part of the study will need to include 44 patients (including the patients recruited in the  
4 dose-finding part of the phase I, allocated at the dose level finally identified as the recommended  
5 dose). If all 44 patients are evaluable at 3 years, the treatment strategy will be considered to be  
6  
7 insufficiently effective if  $\leq 27$  patients are alive without a biochemical relapse at 3 years.  
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11 The operating characteristics of the design are:

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13 ○  $p_0=0.50$ ,  $p_1=0.70$
- 14  
15 ○ Defined Type I error = 0.05 (computed type-I error of the design = 0.048)
- 16  
17 ○ Defined Power = 0.85 (computed power = 0.861)
- 18

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20 If some patient data are censored before 3 years, the 3-year bRFS will be estimated using Kaplan-  
21 Meier method and the lower boundary of the 90% confidence interval will be compared to  $p_0=0.50$ .  
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23 The conclusion will be positive if we can reject the null hypothesis  $p_0=0.50$  at a one-sided 5% alpha  
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25 level.  
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28 To date, no standard local treatment exists for patients with an intraprostatic recurrence after  
29 radiotherapy. A number of treatments options exist including: radical prostatectomy, brachytherapy,  
30 HIFU, cryotherapy, and more recently SBRT. These treatments are associated with a variety of  
31 genitourinary and gastrointestinal toxicities and complications. The literature to date consists mainly  
32 of retrospective and small prospective series making it difficult to assess and compare these  
33 techniques. The phase I part of GETUG-AFU 31 trial will evaluate SBRT dose of 30 Gy in 5 fractions,  
34 over 12 days, and then depending on tolerance, 36 Gy in 6 fractions over 12 days. The latter, 36 Gy in  
35 6 fractions, is the current scheme used at the Oscar Lambret Centre for all repeat SBRT. This dose is  
36 higher than that described by Jereczek-Fossa et al. (30 Gy in 5 fractions),[29] discussed as being too  
37 low,[30] but lower than the dose used by Fuller (38 Gy in 4 fractions) [30]. A lower dose (5 x 5 Gy)  
38 was used in Zerini et al.[32] We have decided to initially use a phase I study, using dose-limiting  
39 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  
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41 of the study. In phase I radiotherapy trials, late complications are often not taken into account and  
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43 there is currently no consensus on the methodology used for these studies. Although most phase I  
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3 radiotherapy studies use a 3+3 design, it is not suitable for these studies as it does not assess late  
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5 toxicity. More complex designs such as the TITE-CRM are recommended, which will shorten the  
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7 duration of the entire trial and efficiently uses patient information throughout the study.[40]  
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### 10 11 **Ethics and dissemination**

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13 The study has been approved by ethics committee "Ile de France III" (2017-A00008-45) for all study  
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15 sites. The findings of this study will be disseminated through peer-reviewed publications and  
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17 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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Ms S. Marchant for writing assistance

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3 **Figures legends**

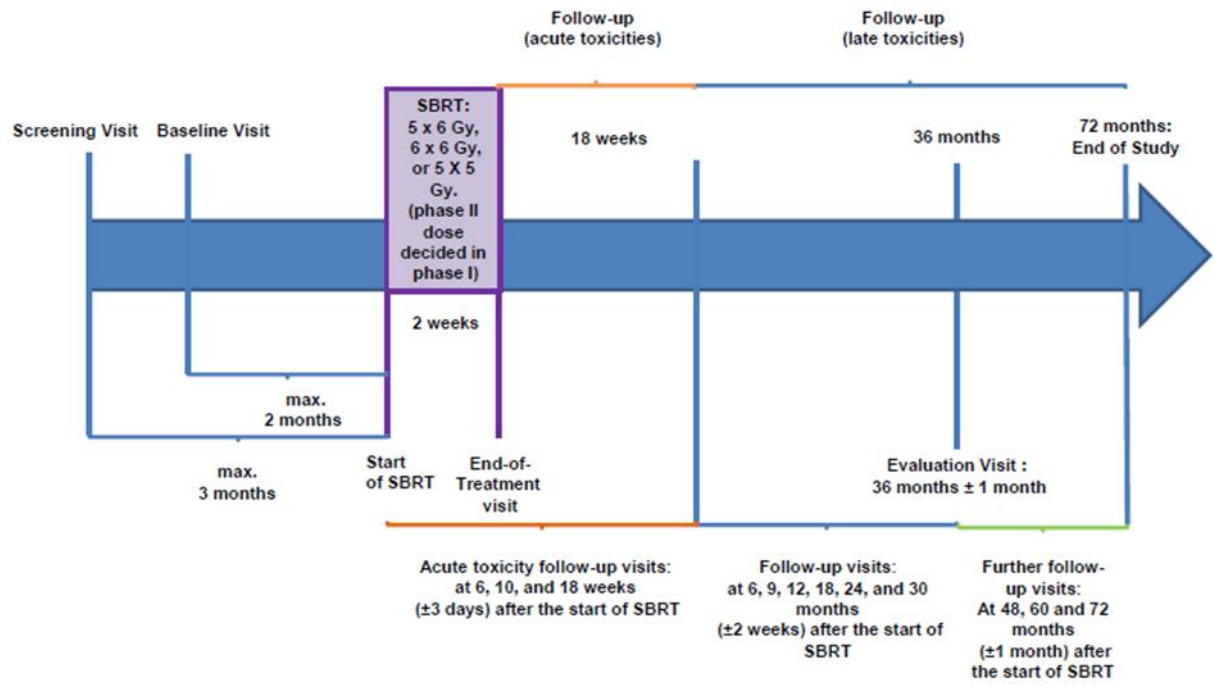
4 Fig. 1 Overview of study flow chart. SBRT: stereotactic body radiotherapy

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7 Fig 2. Detailed description of study flow chart

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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			
				End RT	W6	W10	W14 <sup>1</sup>	W18	M6	M9	M12	M18	M24	M30	M36	M48	M60	M72/End of Study
Visits	ScV	BV																
Eligibility criteria	X	X																
Signed informed consent form	X																	
Enrollment in the study		X																
<b>CLINICAL EXAMINATION</b>																		
Weight, height <sup>2</sup> , PS (WHO)	X	X					X	X	X	X	X	X	X	X	X	X	X	X
Digital rectal examination (clinical stage)	X	X <sup>3</sup>						X		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
<b>QUESTIONNAIRES</b>																		
QLQ-C30 and QLQ-PR25		X						X		X	X	X	X	X	X	X	X	X
IPSS		X					X	X	X	X	X	X	X	X	X	X	X	X
IIEF5		X					X	X	X	X	X	X	X	X	X	X	X	X
<b>LABORATORY TESTS</b>																		
CBC, platelets		X																
PT, PTT, and INR		X																
PSA		X					X		X	X	X	X	X	X	X	X	X	X
<b>PATHOLOGICAL EVALUATION</b>																		
Gleason score; number of positive biopsies, total number of biopsies; total length of cancer on biopsies; total length of biopsies	X																	
<b>PARACLINICAL INVESTIGATION</b>																		
Multi-parametric MRI (pelvic and prostate)	X <sup>2</sup>							X		X		X		X	X	X	X	X
Choline PET scan	X <sup>3</sup>																	
TNM evaluation	X																	
<b>TRANSLATIONAL RESEARCH</b>																		
Prostate tumor biopsies (initial before any treatment and at recurrence before SBRT)		X <sup>6</sup>																

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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  $p(\text{DLT})=0.25$ . 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  $\alpha$  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 ( $p(\text{DLT})=0.25 \pm 0.05$ , i.e. indifference interval: 0.20 to 0.30) and the prior MTD ( $\text{MTD}_0$ ) at the 2<sup>nd</sup> dose level, meaning that the clinicians believe, a priori, that the 2<sup>nd</sup> dose (6 x 6 Gy) is probably the MTD. This yields a vector of prior probabilities  $\{p_{ok}\}$  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  $\alpha$  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:

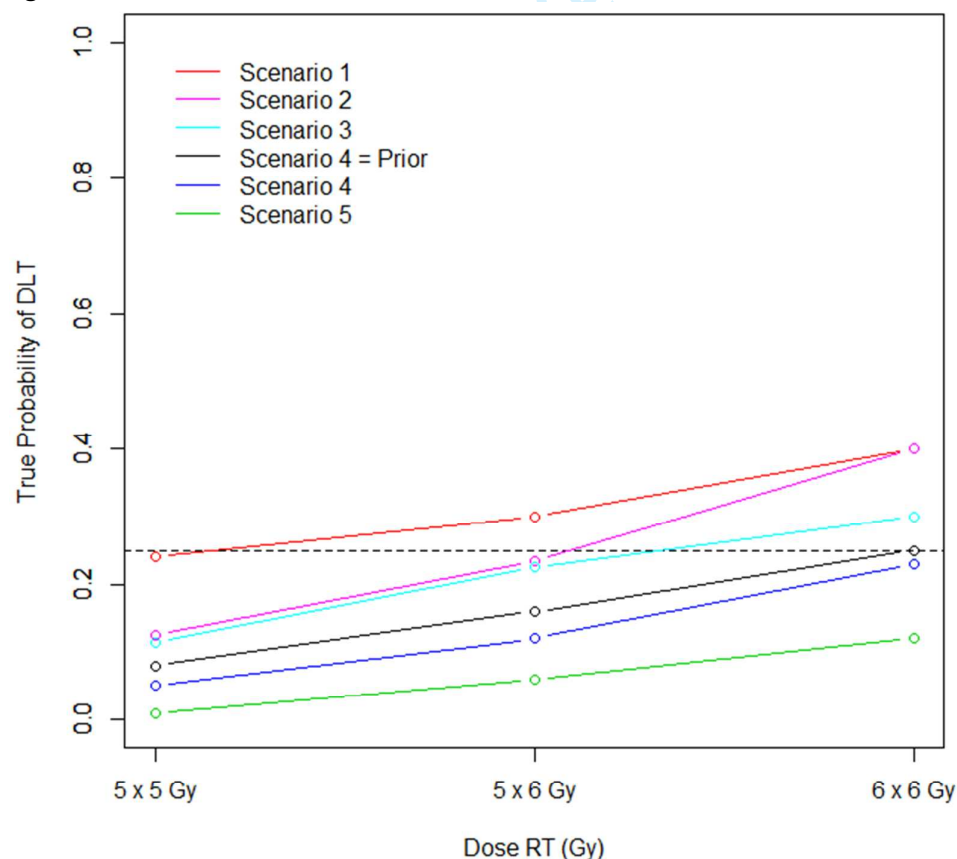
- highly toxic,
- moderately toxic at dose levels -1 and 1, highly toxic at dose level 2
- moderately toxic et every dose level,
- similar with prior probabilities,
- close to the probabilities but a little less toxic,
- little toxic

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
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <a href="#">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)</a>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <a href="#">ClinicalTrials : NCT03438552</a>
	2b	All items from the World Health Organization Trial Registration Data Set <a href="#">IdRCB : 2017-A00008-45</a>
Protocol version	3	Date and version identifier <a href="#">version n°3.0 – 26/08/2016</a>
Funding	4	Sources and types of financial material, and other support  <a href="#">Support by a grant of National Institute of Cancer (INCA)</a>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <a href="#">Docteur David PASQUIER</a> <a href="#">Centre Oscar Lambret - Département de Radiothérapie</a> <a href="#">3, rue Frédéric Combemale - BP307 59020 Lille Cedex</a> <a href="#">Tél : 03.20.29.59.11 - Fax : 03.20.29.58.96</a> <a href="#">E-mail : <u>d-pasquier@o-lambret.fr</u></a>
	5b	Name and contact information for the trial sponsor <b>UNICANCER</b> <a href="#">101 Rue de Tolbiac, 75654 Paris</a> <a href="#">Soazig NENAN +33 (0)185 343 113 s-nenan@unicancer.fr</a> <a href="#">Meryem BRIHOUM +33 (0)1 80 50 12 95 m-brihoum@unicancer.fr</a>



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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

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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

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**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-Salpêtrière, Paris, France  
 Principal Investigator: Philippe MAINGON

ICO -Site René Gauducheau, Saint-Herblain, France  
 Principal Investigator: Stephane SUPLOT

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  $\leq$ 20 ng/mL and Gleason score  $\leq$ 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  $\leq$ 10 ng/mL at baseline (before salvage-SBRT)
9. PSA doubling time  $>$ 10 months
10. International Prostate Cancer Score (IPSS)  $\leq$ 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  $\geq$ 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.

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48	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
22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48	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  <b>Primary Outcome Measure:</b> [ 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  <b>Secondary Outcome Measure:</b> 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
49 50 51 52 53 54 55 56 57 58 59 60	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)

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22	Sample size	14	<p>Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations</p> <p>47 patients</p> <p><b>Sample Size Calculations:</b> 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 <math>p_1=0.70</math>, with a test against <math>p_0=0.50</math> at a one-sided 5%-alpha level.</p>
23 24 25 26	Recruitment	15	<p>Strategies for achieving adequate participant enrolment to reach target sample size</p> <p><a href="#">Communication and follow-up of the participating centers</a></p>

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

31 32 33 34 35 36 37 38	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
39 40 41 42	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
43 44 45 46	Implementation	16c	Who will generate the allocation sequence: who will enrol participants: and who will assign participants to interventions:
47 48 49 50 51 52 53 54 55 56 57 58 59 60	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how <a href="#">Not applicable</a>
		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial <a href="#">Not applicable</a>

## 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 <a href="#">Describe in protocol and data management procedures</a>
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) <a href="#">Not applicable</a>
	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) <a href="#">Not applicable</a>

## 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 <a href="#">Coordinator : validate the risk analysis (LIR) and the monitoring plan</a> <a href="#">Project Manager : determine the risk analysis (LIR) and write the monitoring plan</a> <a href="#">Clinical Research Associate (CRA) :perform monitoring according the monitoring plan</a>
	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

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2	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
3			spontaneously reported adverse events and other unintended effects of trial
4			interventions or trial conduct
5			<a href="#">This point is provided by the vigilance unit of the sponsor. All details are described</a>
6			<a href="#">in the protocol</a>
7			
8	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the
9			process will be independent from investigators and the sponsor
10			<a href="#">Actually and according the risk analysis, no audit is planned</a>
11			
12	<b>Ethics and dissemination</b>		
13			
14	Research ethics	24	Plans for seeking research ethics committee/institutional review board
15	approval		(REC/IRB) approval
16			<a href="#">N° IdRCB : 2017-A00008-45</a>
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18			<a href="#">Initial Approval by CPP Nord-Ouest I (Committee for the Protection of</a>
19			<a href="#">Personnes/Ethic committee) : 25/07/2017</a>
20			<a href="#">Approval Number: CPP3517-I</a>
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22	Protocol	25	Plans for communicating important protocol modifications (eg, changes to
23	amendments		eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators,
24			REC/IRBs, trial participants, trial registries, journals, regulators)
25			<a href="#">Each major protocol amendment is submitted to authorities for approval.</a>
26			<a href="#">After approval, it is communicated to all the actors of this project (investigators,</a>
27			<a href="#">trial centers, trial registry ...)</a>
28			
29	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants
30			or authorised surrogates, and how (see Item 32)
31			<a href="#">Principal Investigator or sub-investigator</a>
32			
33		26b	Additional consent provisions for collection and use of participant data and
34			biological specimens in ancillary studies, if applicable
35			<a href="#">Not applicable</a>
36			
37	Confidentiality	27	How personal information about potential and enrolled participants will be
38			collected, shared, and maintained in order to protect confidentiality before,
39			during, and after the trial
40			<a href="#">Collected by investigators and CRA on each trial centers. These data are</a>
41			<a href="#">anonymized.</a>
42			<a href="#">Shared on the eCRF.</a>
43			<a href="#">There is a control access on the eCRF</a>
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46	Declaration of	28	Financial and other competing interests for principal investigators for the
47	interests		overall trial and each study site
48			<a href="#">None</a>
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50	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure
51			of contractual agreements that limit such access for investigators
52			<a href="#">Directly on the eCRF</a>
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2	Ancillary and post-	30	Provisions, if any, for ancillary and post-trial care, and for compensation to
3	trial care		those who suffer harm from trial participation
4			<a href="#">Not applicable</a>
5			
6	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
7	policy		participants, healthcare professionals, the public, and other relevant groups
8			(eg, via publication, reporting in results databases, or other data sharing
9			arrangements), including any publication restrictions
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11			A publication is planned; no publication restriction.
12			
13		31b	Authorship eligibility guidelines and any intended use of professional writers
14			
15			Coordinator will be the first author; co investigators will be authors.
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19		31c	Plans, if any, for granting public access to the full protocol, participant-level
20			dataset, and statistical code
21			
22			N/A
23			
24	<b>Appendices</b>		
25			
26	Informed consent	32	Model consent form and other related documentation given to participants
27	materials		and authorised surrogates
28			
29			
30	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
31	specimens		specimens for genetic or molecular analysis in the current trial and for future
32			use in ancillary studies, if applicable
33			
34			<a href="#">Not applicable</a>

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\*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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026666.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Apr-2019
Complete List of Authors:	Pasquier, David; Centre Oscar Lambret, Le Deley, Marie-Cécile; Centre Oscar Lambret, Methodology and Biostatistic Unit; Université Paris-Sud, Université Paris-Saclay, CESP, INSERM, Faculté de médecine Tresch, Emmanuelle; Centre Oscar Lambret, Methodology and Biostatistic Unit Cormier, Luc; Centre Hospitalier Universitaire de Dijon Duterque, Martine; Institut de Biologie de Lille Nenan, Soazig; UNICANCER Lartigau, eric; Centre Oscar Lambret
<b>Primary Subject Heading</b>:	Oncology
Secondary Subject Heading:	Urology
Keywords:	prostate cancer, stereotactic body radiation therapy, recurrent prostate cancer, salvage radiotherapy

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Manuscripts

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3 1 **GETUG-AFU 31: a phase I/II multi-center study evaluating the safety and efficacy of salvage**  
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5 2 **stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation**  
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7 3 **therapy; study protocol**  
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12 5 David Pasquier<sup>1,2</sup>, Marie Cécile LeDeley<sup>3</sup>, Emmanuelle Tresch<sup>3</sup>, Luc Cormier<sup>4</sup>, Martine Duterque<sup>5</sup>,  
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10 30 Word count : 5193  
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## 14 32 **ARTICLE SUMMARY**

15  
16 33 Introduction. Prostate cancer is the third most important cancer in terms of mortality in men. No  
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18 34 standard local treatment exists for patients with an intraprostatic recurrence after radiotherapy.  
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20 35 Stereotatic body radiotherapy (SBRT) could be a curative treatment for local recurrence.  
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23 36 Methods and Analysis. We plan to perform a multicenter prospective phase I/II study including at  
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25 37 least 47 patients. Eligible patients are patients with biochemical recurrence occurring at least 2 years  
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27 38 after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2  
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29 39 ng/mL):  
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32 40 T1–T2c and PSA  $\leq 20$  ng/mL and Gleason score  $\leq 7$  at initial diagnosis before the initial/first  
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34 41 treatment;

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36 42 Recurrence of prostatic adenocarcinoma proven by histology following radiotherapy by  
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38 43 transrectal or transperineal sextant biopsies of the two lobes of the prostate, with a minimum of  
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40 44 12 biopsies, irrespective of Gleason score;

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42 45 Clinical stage T1-T2 on relapse;

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44 46 Pelvic and prostatic assessment by multiparametric MRI;

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46 47 Absence of pelvic or metastatic recurrence proven by choline or PSMA PET scan;

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48 48 PSA level  $\leq 10$  ng/mL at baseline (before salvage-SBRT), PSA doubling time  $> 10$  months, IPSS  $\leq 12$ .  
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50  
51 49 The phase I primary objective is the selection of the recommended dose for salvage-SBRT (5 x 6 Gy, 6  
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53 50 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity. The dose of salvage-SBRT will be selected using a  
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55 51 Time-to-Event Continual-Reassessment-Method based on dose-limiting toxicity defined as grade  $\geq 3$   
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57 52 gastrointestinal or urinary toxicity or any other grade 4 adverse event. The phase II primary objective  
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3 53 is to estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate.

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5 54 Phase II secondary objectives are: acute and late toxicities, quality of life, clinical progression free  
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7 55 survival and overall survival.

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10 56 Ethics and Dissemination. The study has received ethical approval from the Ethics committee "Ile-de-  
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12 57 France III". Academic dissemination will occur through publication and conference presentations.

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14 58 **Trial registration:** NCT03438552

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16 59 **Date of trial registration:** November 14, 2017

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21 61 **Strengths and limitations of this study funding**

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23 62 - Very innovative trial evaluating stereotactic body radiotherapy for recurrent prostate cancer,  
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25 63 the only ongoing trial of this kind to our knowledge

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27 64 - Clinical trial supported by the GETUG-AFU cooperative group, expert in the field, and funded  
28  
29 65 by the French National Cancer Institute (INCa)

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31 66 - Time-to-Event Continual Reassessment Method, a more appropriate method than the 3+3  
32  
33 67 design to quantify late toxicity in phase I radiotherapy trials

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35 68 - Proof-of-concept study; therefore, further research will be required

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41 70 **Keywords:** prostate cancer, stereotactic body radiation therapy, recurrent prostate cancer

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## 74 **Background**

75 Prostate cancer is the third most important cancer in terms of mortality in men (after lung and  
76 colorectal cancer), and the fourth leading cancer overall [1]. In the European Union, it was predicted  
77 that 72600 patients would die from prostate cancer in 2015. The rate of recurrence/relapse of  
78 prostate cancer after primary external beam radiotherapy varies from 21% to 65% depending on the  
79 study [2,3]. Zelefsky et al. performed biopsies on 339 patients after treatment with 3-dimensional  
80 conformal radiotherapy (3D-CRT) or intensity modulated RT for T1c-T3 stage prostate cancer, with a  
81 minimum follow-up of 2.5 years [2]. They found that the rate of positive biopsy according to  
82 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  
83 years biopsy was performed in 312/843 patients included in MRC RT01 trial. A positive biopsy was  
84 prognostic of worse biological progression free survival compared with negative and suspicious  
85 biopsies, hazard ratio (HR)=4.81 (95% confidence interval [CI]: 2.50-9.26, p<0.001). The estimate for  
86 survival was HR=1.58 (95% CI: 0.52-4.78, p=0.42).

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

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

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3 100 specific mortality rate of 36% vs. 6% ( $p=0.0001$ ). Thus late relapse and long PSA doubling time are  
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5 101 prognostic factors of solely intraprostatic relapse.

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7 102 Prostate-specific antigen (PSA) is a validated biomarker for prostate cancer. PSA levels are  
8  
9 103 extensively used to monitor response to radical prostatectomy (RP) and external-beam radiotherapy  
10 104 (EBRT). The serum PSA level is an important surrogate for recurrence in prostate cancer patients. The  
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12 105 recommendations of the Radiation Therapy Oncology Group (RTOG) ASTRO Phoenix Consensus  
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14 106 Conference suggested that an increase of  $\geq 2$  ng/mL from the nadir be used to define  
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16 107 recurrence/relapse [6]. It is important to note that biochemical recurrence may indicate local or  
17  
18 108 systemic disease recurrence, and may require prostate biopsy for confirmation particularly when  
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20 109 local salvage treatments are being considered [7].

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23 110 A number of different salvage treatments have been used after failure of primary radiotherapy.  
24  
25 111 RP is more invasive than brachytherapy, ultrasound, high-intensity focused ultrasound (HIFU), and  
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27 112 SBRT. Below is a brief discussion of the results obtained with each techniques and its associated  
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29 113 toxicity and complications.

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32 114 Salvage RP (SRP) is a treatment option after local recurrence following EBRT. However, the  
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34 115 morbidity, including incontinence and erectile dysfunction, is higher than that observed with first-line  
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36 116 RP patients. A systematic literature review [7] reported that the probability of biochemical relapse–  
37  
38 117 free survival (bRFS) following SRP in prostate cancer patients was 47-82% after 5 years and 28-53%  
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40 118 after 10 years. SRP has an increased risk of adverse events due to fibrosis and poor wound healing  
41  
42 119 after radiotherapy. Furthermore, SRP after radiotherapy compared to primary RP has a significantly  
43  
44 120 higher rate of urinary and gastrointestinal morbidity [8]. The review above [7], reported that the  
45  
46 121 most frequent complications were anastomotic stricture (7-41%) and rectal injury (0-28%). The  
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48 122 majority (50-91%) of men had erectile dysfunction before SRP and 80-100% after surgery. Post-  
49  
50 123 operative urinary continence ranged from 21-90%.

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52 124 In a recent review, salvage brachytherapy after EBRT is reported to achieve biochemical control  
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54 125 rates of 20% to 89% (median follow-up: 19 to 108 months) [9]. Rates of genitourinary toxicities range  
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3 126 from 12% to 87% for grade 1-2, and 3% to 47% for grade 3-4 toxicities. Similarly, the rates of  
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5 127 gastrointestinal toxicities range from 4% to 65% for grade 1-2, and 0% to 20% for grade 3-4 toxicities.  
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7 128 Erectile dysfunction was observed in 2% to 95% of men. A phase II study of salvage high-dose-rate  
8  
9 129 brachytherapy (HDR) for treating recurrent prostate cancer after definitive external beam  
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11 130 radiotherapy was reported by Yamada [10]. The 42 patients enrolled, with biopsy proven recurrence,  
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13 131 were treated with salvage HDR (iridium-192) with a resulting bRFS at 5 years of 68.5% (median  
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15 132 follow-up of 36 months [range: 2-66 months]). Acute genitourinary toxicity was observed: grade 1,  
16  
17 133 38% of patients and grade 2: 40%. Similarly, late genitourinary toxicity was observed: grade 1, 38% of  
18  
19 134 patients and grade 2, 48%. In addition, 1 patient had a grade 3 urinary incontinence and 3 had grade  
20  
21 135 3 urethral strictures. Late gastrointestinal toxicities were observed: grade 1, 43% of patients and  
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23 136 grade 2, 14%. More recently, a study of 83 prostate cancer patients with local recurrence after  
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25 137 radiotherapy treated with high-dose-rate brachytherapy was reported [11]. The 3-year and 5-year  
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27 138 bRFS were 76% and 67%. A phase II study of the RTOG in 100 patients was recently presented: twelve  
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29 139 (14%) experienced late grade 3 genitourinary/gastrointestinal adverse effects. This rate of late grade  
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31 140 3 toxicity (14%) was not unacceptable by the predetermined protocol specification, without any  
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33 141 grade 4-5 events. The only factor predictive of late toxicity was implant dose, underlining the need  
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35 142 for meticulous planning and technique to limit the final delivered dose [12]. In France, a phase II  
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37 143 study, "Brachytherapy for Recurrent Prostate Cancer" (CAPRICUR) was recently completed [13].  
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43 144 HIFU is another less invasive salvage treatments following recurrence. HIFU uses focused  
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45 145 ultrasound to generate heat (85°C) which induces tissue necrosis [14]. The following studies have  
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47 146 investigated the use of salvage-HIFU after initial radiotherapy. A French group treated 290 men with  
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49 147 biopsy-confirmed recurrent prostate cancer, after radiotherapy, with salvage HIFU [15]. At 7 years,  
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51 148 the cancer-specific survival rate was 80% and the metastasis-free survival rate was 79.6%. Recto-  
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53 149 urethral fistula occurred in 0.4% of patients and 19.5% had grade 2/3 incontinence. Half of the  
54  
55 150 patients also received hormone therapy. Survival without relapse at 5 years after HIFU, by D'Amico  
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57 151 risk groups prior to their initial treatment, was 45% (favorable), 31% (intermediate risk) and 21%  
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3 152 (high risk). In this cohort, the grade  $\leq 3$  urinary incontinence levels were 23% (favorable), 14%  
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5 153 (intermediate risk) and 9% (high risk). Nearly 8% of patients required an artificial sphincter following  
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7 154 HIFU. Importantly, pubic osteitis occurred in 2.5% of patients despite adherence to parameters  
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9 155 specific to HIFU following radiotherapy [15].

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12 156 Cryotherapy is thermo-ablative treatment; the third-generation argon/helium-based cryotherapy  
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14 157 system creates precise isotherms through ultrathin needles [16]. In a retrospective multicenter series  
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16 158 pooling 279 patients, survival without biochemical relapse at 5 years was 54%. Prostatic biopsies  
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18 159 showed tumor persistence in 32% of patients following cryotherapy [17]. In a paired case-controlled  
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20 160 study, prostatectomy and cryotherapy were compared following radiotherapy. Survival without  
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22 161 relapse (PSA nadir + 0.4 ng/mL) at 5 years was significantly lower after cryotherapy (21% vs. 61%,  
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24 162  $p < 0.001$ ); this was confirmed by the 5-year OS rate of 85%, cryotherapy, vs 95%, radical  
25  
26 163 prostatectomy ( $p = 0.001$ ) [18]. Intermediate results from a study investigating third-generation  
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28 164 cryotherapy as a salvage treatment of locally recurrent prostate cancer after radiotherapy was  
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30 165 published [19]. The 5-year bRFS rate (Phoenix definition) was 43.5% and with a 5-year OS rate of  
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32 166 92.3%. Mild complications (grades 1 and 2) were reported including: mild incontinence (9.4%), acute  
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34 167 rectal pain (31.3%), lower urinary tract symptoms (15.6%) and erectile dysfunction (57.1%). Grade 3  
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36 168 toxicities: incontinence (3.1%) and urethral sloughing (3.1%) were observed.

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39 169 Androgen-deprivation therapy (ADT) alone (continuous or intermittent) is commonly given to  
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41 170 patients with biochemical relapse after radiotherapy [20]. In a series based on data from a North  
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43 171 American national registry (CaPSURE), 71% of patients were treated for biochemical relapse after  
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45 172 prostatectomy or radiotherapy. ADT was initiated in 93% of these patients, and the remaining  
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47 173 patients were treated with surgery, brachytherapy, cryotherapy, or repeat external radiotherapy  
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49 174 [21]. ADT may cause adverse effects impacting patient's quality of life (including: hot flushes, erectile  
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51 175 dysfunction and reduced libido, cognitive impairment, and anemia). The metabolic changes  
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53 176 associated with hormone therapy may also increase the risk of cardiovascular morbidity. The  
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55 177 reduction in bone mass is maximal in the first year and increases with the duration of castration; the  
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3 178 risk of fracture is increased in patients surviving for more than 5 years [22-23]. The guidelines suggest  
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5 179 that a simple follow-up can be implemented for local recurrence in patients with a limited life  
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7 180 expectancy or for those who do not wish to undergo local salvage treatment. The last European  
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10 181 Association of Urology guidelines [24] recommended to perform salvage surgery in experienced  
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12 182 centres due to the increased rate of side effects. It is recommended to offer/discuss HIFU,  
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14 183 cryosurgical ablation and salvage brachytherapy to/with patients without evidence of metastasis and  
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16 184 with histologically proven local recurrence and to inform patients about the experimental nature of  
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19 185 these approaches. The level of evidence for each of these recommendations is 3 [24].

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21 186 SBRT delivers highly conformal, high-dose radiation in a few fractions (hypofractionation), typically  
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23 187 5 to 7 fractions for prostate cancer. It is reported that tissues with a low  $\alpha/\beta$  ratio, as for prostate  
24  
25 188 cancer, are more sensitive to large doses of radiation per fraction. The surrounding normal tissue  
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27 189 could have similar or higher  $\alpha/\beta$  ratio. This suggests that hypofractionation (large radiation dose per  
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29 190 fraction) may result in improved tumor control with limited toxicity. A pooled analysis of 1100  
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32 191 patients included in separate prospective phase II studies in 8 institutions was performed to evaluate  
33  
34 192 the effectiveness of SBRT as a first-line treatment for localized prostate cancer [25]. The SBRT was  
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36 193 delivered by CyberKnife with a median dose of 36.25 Gy in 4-5 fractions. The 5-year bRFS rate was  
37  
38 194 93% for all patients. Thus relapse-free survival rates after SBRT compare favourably with other  
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40 195 definitive treatments for low and intermediate-risk patients with a short follow up. SBRT is well  
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42 196 tolerated with a low effect on quality of life [25-28]. In addition sexual function appeared to be  
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45 197 spared in the majority of patients [25-28].

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48 198 SBRT has also been used as a salvage treatment following failure of external radiotherapy.  
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50 199 Jereczek-Fossa et al. published data on 34 consecutive patients treated with robotic SBRT for isolated  
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52 200 recurrent primary, lymph node, or metastatic prostate cancer [29]. Of the 34 patients, 15 patients  
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54 201 had intraprostatic recurrence, confirmed by biopsy, and were treated with SBRT (CyberKnife) with a  
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56 202 median dose of 30 Gy in 5 fractions. Fourteen patients showed a biochemical response; the median  
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58 203 survival without recurrence was 13 months. Five patients presented a clinical relapse, including one  
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3 204 new intraprostatic recurrence. Urinary toxicity was low, with a grade 3 urinary toxicity in only one  
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5 205 patient. No case of acute or late gastrointestinal toxicity was reported. This good gastrointestinal  
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7 206 tolerability has subsequently been confirmed [29-32]. In Fuller et al twenty-nine patients were  
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10 207 treated in a phase II trial with stereotactic radiotherapy for intraprostatic recurrence [30]. Eligible  
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12 208 patients had to present biopsy-proven intraprostatic recurrence graded T1 to T3N0M0 more than 2  
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14 209 years post-radiotherapy and without a pre-existing grade >1 radiotherapy toxicity. The prior median  
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16 210 dose delivered was 73.8 Gy and the median interval between the treatments was 88 months. The  
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18 211 dose delivered to the entire gland was 34 Gy in five fractions over 5 days (heterogeneous  
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20 212 intraprostatic dose of up to 50 Gy). With a median follow-up of 24 months, survival without  
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22 213 recurrence was 82%. Toxicity was acceptable, with 18% grade  $\geq 2$  urinary toxicity, including one  
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24 214 patient with a grade 4 toxicity, and no late gastrointestinal toxicity above grade 1. Particular  
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26 215 attention should be given to patients who still exhibit urinary toxicity after initial radiotherapy [30].  
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28 216 Our preliminary retrospective results in 23 patients treated for this indication were published  
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30 217 recently [31]. A total dose of 36 Gy was prescribed in 6 fractions of 6 Gy. Nineteen patients had a  
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32 218 whole-gland and four a partial treatment. Median follow-up was 23 months (range 6 to 40 months).  
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34 219 We observed no grade 4 or 5 toxicity. Two patients presented grade 3 toxicities. Others toxicities  
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36 220 include urinary (5 grade 2 and 9 grade 1) and rectal toxicities (2 grade 2 and 2 grade 1). The dose  
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38 221 levels selected in our study are close to those used in de novo patients, and the same as those  
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40 222 described in retrospective salvage treatment series. These schemes seem to provide an acceptable  
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42 223 compromise between efficacy and toxicity but have not been evaluated prospectively.

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47 224 To date, no standard local treatment exists for patients with an intraprostatic recurrence after  
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49 225 radiotherapy [33]. A number of treatments options exist including: radical prostatectomy,  
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51 226 brachytherapy, HIFU, cryotherapy, and stereotactic radiotherapy. The literature to date consists  
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53 227 mainly of retrospective and small prospective series making it difficult to assess and compare these  
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55 228 techniques. In recent years, SBRT has been used to treat localized prostate cancer in the primary  
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57 229 setting but also as a salvage treatment after failure of radiotherapy. The initial results of these  
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3 230 retrospective studies are promising, with respect to survival and tolerance, but further studies are  
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5 231 required to confirm these initial results. Our proposed study will provide further evidence of SBRT as  
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7 232 a supplementary non-invasive curative treatment for local recurrence following radiotherapy. This  
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9 233 study could provide the foundation for prospective studies comparing the available salvage  
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11 234 treatments after radiotherapy.  
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### 16 236 **Methods/design**

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18 237 This study is approved by the Ethics committee "Ile de France III" (2017-A00008-45) and is registered  
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20 238 on clinicaltrials.gov (NCT03438552). This multicenter open-labelled phase I/II study will initially select  
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22 239 the SBRT scheme (phase I), either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy. The effectiveness of SBRT scheme  
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24 240 selected in phase I will then be evaluated in a single-arm multicenter phase II study.  
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28 241 PHASE I primary objective and assessment:

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30 242 Selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on  
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32 243 dose-limiting toxicity observed during the 18 weeks following the initiation of salvage-SBRT. The dose  
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34 244 of salvage-SBRT will be selected using a Time-to-Event Continual Reassessment Method [34-36]  
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36 245 based on dose-limiting toxicity defined as grade  $\geq 3$  gastrointestinal or urinary toxicity or any other  
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38 246 grade 4 adverse event observed during the 18 weeks following the initiation of salvage-SBRT.  
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41 247 PHASE II primary objective and assessment:

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43 248 Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate (Phoenix  
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45 249 definition: increase in serum total PSA  $\geq 2$  ng/mL above the nadir). Time to biochemical relapse-free  
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47 250 survival will be computed from registration. Patients alive without biochemical progression at the  
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49 251 time of the analysis will be censored at the last follow-up date. In the event of death, whatever the  
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51 252 cause of death, the patient will be considered as a failure.  
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54 253 PHASE II secondary objective(s) and assessment:  
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3 256      ○ Acute and late genitourinary and gastrointestinal toxicities over the first 3 years according to  
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5 257      the NCI-CTCAE V4.03 classification (June 14th, 2010), International prostate Symptom Score  
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7 258      (IPSS) score for urinary symptoms, and International Index of Erectile Function (IIEF5) for  
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10 259      erectile function. Patients will be followed for 5 years after salvage SBRT to assess late  
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12 260      toxicity. Patients with second biochemical recurrence will not be excluded in order to assess  
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14 261      late toxicity.
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16 262      ○ Quality of life will be evaluated based on the EORTC QLQ-C30 and QLQ-PR25 scales. The Time  
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18 263      Until Definitive Deterioration (TUDD) will be computed from registration until the first  
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20 264      observation of a definitive deterioration of the quality of life, defined as a score decreased by  
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22 265      10 points (in the case of global health scale and functional scales) or increased by 10 points  
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24 266      (in the case of symptom scales) compared to the score at baseline, without later  
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26 267      improvement superior to 10 points compared to baseline score.
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28 268      ○ Clinical progression-free survival is defined as the time interval between the date of  
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30 269      registration and the date of clinical progression (local progression assessed by the physical  
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32 270      examination, or appearance of metastatic lesions) or death irrespective of the cause.
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34 271      ○ Overall survival is defined as the time interval between the date of registration and the date  
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36 272      of death irrespective of the cause.
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38 273      ○ Erythroblast transformation-specific related gene (ERG) fusion expression will be evaluated  
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40 274      using immunohistochemistry (IHC) tests. ERG fusion and androgen-receptor splice variant 7  
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42 275      (ARV7) expression will be evaluated on biopsies before the first radiotherapy treatment (at  
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44 276      diagnosis, if available) and before salvage radiotherapy after biochemical recurrence.
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52 278      **DIAGNOSIS AND INCLUSION CRITERIA:**

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54 279      ○ Biochemical recurrence occurring at least 2 years after external radiotherapy  
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56 280      for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2  
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58 281      ng/mL)
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- T1–T2c and PSA  $\leq 20$  ng/mL and Gleason score  $\leq 7$  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  $\leq 10$  ng/mL at baseline (before salvage-SBRT)
  - PSA doubling time  $> 10$  months
  - IPSS  $\leq 12$
  - 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

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3 308 ○ Life-expectancy greater than or equal to 5 years (Lee scale)  
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5 309 ○ Patient registered with a health insurance system  
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7 310 ○ Patient who has signed the informed consent form  
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10 311 ○ Patients willing and able to comply with the scheduled visits, treatment plan,  
11  
12 312 laboratory tests, and other study procedures indicated in the protocol.  
13

14 313 EXCLUSION CRITERIA:

- 15  
16 314 ○ Lymph node or metastatic spread  
17  
18 315 ○ Late post-radiotherapy urinary or gastrointestinal toxicity of grade  $\geq 2$   
19  
20 316 (following primary radiotherapy)  
21  
22  
23 317 ○ Other cancers in the last 5 years except for non-melanoma-type skin cancer  
24  
25 318 ○ History of inflammatory bowel disease  
26  
27 319 ○ Anticoagulant treatment  
28  
29  
30 320 ○ Contraindications to undergoing MRI  
31  
32 321 ○ Prostate volume > 80 cc  
33  
34 322 ○ Transurethral resection of the prostate (TURP) in the 6 months before  
35  
36 323 registration  
37  
38  
39 324 ○ Presence of rectal telangiectasia grade 3 classified by the Vienne Rectoscopy  
40  
41 325 Score (obligatory rectoscopy) [37,38]  
42  
43 326 ○ Previous rectal surgery  
44  
45 327 ○ Patients unable to undergo medical follow-up in the study for geographical,  
46  
47 328 social or psychological  
48  
49  
50 329 ○ Person deprived of their liberty or under protective  
51

52 330 INTERVENTION

53  
54 331 A flow chart presenting the different steps from inclusion until treatment is presented in Fig. 1.  
55  
56 332 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  
57  
58 333 delivered over a maximum of 12 days to provide a total dose of 25 to 36 Gy. This radiotherapy may  
59  
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2  
3 334 be administered with the CyberKnife® or a linear accelerator allowing stereotactic radiotherapy. The  
4  
5 335 patient will be placed in a stable and reproducible supine position. Intraprostatic markers (fiducials)  
6  
7 336 will be implanted before the dosimetric CT-scan and MRI are performed. The choice of markers is left  
8  
9  
10 337 to the discretion of each participating site (gold seeds, etc.). The site needs to ensure that the  
11  
12 338 repositioning of the prostate is precise ( $\leq 2$  mm), allowing an exact overlay between dosimetric MRI  
13  
14 339 and computed tomography (CT)-scan. The implant of fiducials is obligatory irrespective of the  
15  
16 340 stereotactic radiotherapy technique used. The fiducials can be implanted during or after the biopsies.  
17  
18 341 The CT-scans and MRIs registration is guided by the fiducials. Each team can choose the fiducials  
19  
20 342 visible on the MRI they wish to use and/or integrate a specific sequence during the centering MRI for  
21  
22 343 better visualization.

23  
24  
25 344 An mpMRI and CT-scan will be carried out at least one week after fiducial implantation. CT-scan  
26  
27 345 images should be acquired with the patient in the treatment position using the chosen immobilizing  
28  
29 346 system, if required according to centers' standard procedures. An intravenous injection of a contrast  
30  
31 347 product should be administered unless contraindicated. Acquisition should allow anatomical  
32  
33 348 structures and markers (already implanted in the prostate) to be visualized. The bladder will be half-  
34  
35 349 filled (neither full nor empty, i.e. a final voiding 90 minutes before the CT-scan followed by ingestion  
36  
37 350 of 250-350 mL of water). The rectum will be empty and not distended. If necessary rectal enema can  
38  
39 351 be used before CT-scan acquisition. Contiguous CT-scan slices  $\leq 2$  mm thick will be taken between the  
40  
41 352 L5-S1 joint space and the small trochanters. After image transfer to a planimetric console, fiducial-  
42  
43 353 based registration with the prostatic mpMRI will take place in order to provide a better definition of  
44  
45 354 the Gross Target Volume (GTV) and prostatic contours, especially the apex. Fiducial-based CT-MRI  
46  
47 355 registration is mandatory. Multimodality image registration with Choline PET is possible but not  
48  
49 356 mandatory.

50  
51  
52 357 Delineation of the target volume will be carried out by a radiotherapist experienced in the  
53  
54 358 definition of prostate volumes on CT-scans and MRIs. The mpMRI-defined contour will be integrated  
55  
56 359 with the CT-scan derived contours in order to define tumor and the prostatic apex more precisely.  
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3 360 GTV will be represented by lesion defined on the multiparametric MRI +/- choline PET; a 5-7 mm  
4  
5 361 margin around the GTV will be used to define the Clinical Target Volume (CTV). CTV is contained in  
6  
7 362 the prostate, except in the case of extracapsular extension (unilateral extracapsular extension on MRI  
8  
9 363 permitted except posteriorly relative to the rectum). In the case where the positive biopsy(ies) are  
10  
11 364 outside and adjacent to the visible lesions on the MRI, the zone containing these biopsies must be  
12  
13 365 included in the CTV so that the prostate cancer recurrence not visible on the MRI is included in the  
14  
15 366 CTV. If no lesion is visible on the MRI and/or choline PET, the zone containing positive biopsies must  
16  
17 367 be included in the CTV. For example: MRI +/-choline PET lesion in 3p and 4p according to ESUR  
18  
19 368 guidelines, with positive biopsies in 1p, 3p and 4p: CTV = MRI GTV + 5 mm + the posterior right base.  
20  
21 369 The total CTV should not be more than half of the total volume of the prostate by MRI. The planning  
22  
23 370 target volume (PTV) will be obtained by an expansion of 2 mm around the CTV in this repeat  
24  
25 371 radiotherapy context. This margin involves that the probability of coverage at 25, 30, or 36 Gy is low,  
26  
27 372 so the reporting will include D2%, 50%, D98% and D95% to describe as much as possible delivered  
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29 373 dose. Organs at risk constraints are specified in Table 1. Daily image guided radiation therapy is  
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31 374 mandatory, intra fraction tracking is recommended.  
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Rectum	Bladder	Urethra + 3 mm
V27 Gy <2 cc	V27 Gy <5 cc	V24 Gy <30%
V12 Gy <20%	V12 Gy <15%	D <sub>max</sub> (35 mm <sup>3</sup> ) <39 Gy
		V36 Gy <1 cc

376

377 Table 1. Organs at risk constraints

378

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



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3 383 which will be centralized in order to verify that the constraints are being observed. For each site, the  
4  
5 384 dosimetric data will be subject to a centralized review prior to SBRT administration in order to verify  
6  
7 385 that constraints are being observed. Follow-up visits are described in Figures 1 and 2.  
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10 386

#### 11 387 SAMPLE SIZE CALCULATION

12 388 Required number of patients to be included: minimum 47 patients. The total sample size will depend  
13  
14 389 upon the number of patients allocated at the different dose levels in the dose-finding parts of the  
15  
16 390 trial. A minimum of 13 patients will be recruited before the expansion phase is open (Phase II part). A  
17  
18 391 total of 44 patients allocated at the recommended dose (recruited in the dose-escalation stage or in  
19  
20 392 the expansion phase) and evaluable at 3 years are required for the main analysis of the Phase II part  
21  
22 393 of the trial to ensure an 85%-power if 3-year bRFS is  $p_1=0.70$ , with a test against  $p_0=0.50$  at a one-  
23  
24 394 sided 5%-alpha level.  
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#### 31 396 STATISTICAL CONSIDERATIONS

##### 32 397 PHASE I

33  
34 398 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  
35  
36 399 level is 5 x 6 Gy. The lower dose level, 5 x 5 Gy, will be considered if excessive toxicity is reported at  
37  
38 400 the first dose-level (5 x 6 Gy). A TimeTo Event-Continuous Reassessment Method (TITE-CRM) with an  
39  
40 401 empiric dose-toxicity model in a Bayesian framework will be used for the dose-finding part of the trial  
41  
42 402 to identify the recommended dose. The target dose limiting toxicity (DLT) probability is set at  
43  
44 403  $p(DLT)=0.25$ . Observations of patients who have no DLT at the time of the analysis but have not  
45  
46 404 completed the DLT assessment period will be down-weighted in the likelihood, proportionally to the  
47  
48 405 length of follow up; for instance, if the last patient has been recruited 8 weeks before a new patient  
49  
50 406 is available for enrolment, and is evaluated at week 10 with no DLT, then his observation is attributed  
51  
52 407 a weight of  $10/18=0.56$ .  
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3 408 At least three patients will be enrolled at the first dose-level and fully evaluated over the 18-week  
4  
5 409 study period before the dose is escalated to the next dose-level. Radiation dose levels for further  
6  
7 410 patients will be defined based on the estimate of the probability of DLT at each dose-level  
8  
9 411 considering all available information accumulated so far. Patients will be treated at the best current  
10  
11 412 estimate of the recommended dose i.e. the dose associated with an estimated probability of DLT the  
12  
13 413 closest to the target 0.25. Patients may eventually be treated at a dose below the dose  
14  
15 414 recommended by the model for safety reasons. The patients can be recruited with no minimal time  
16  
17 415 interval between successive inclusions. During the dose-escalation part of the trial, safety data will  
18  
19 416 have to be reported in the data base in real time. A monthly teleconference meeting with the  
20  
21 417 participation of the biostatistician, the trial coordinator and a representative of the sponsor, to  
22  
23 418 summarize toxicity observations and define the dose to be allocated to the next patient(s) will be  
24  
25 419 held. Safety data will be discussed with an Independent Data Monitoring Committee (IDMC) at the  
26  
27 420 end of the dose-escalation part of trial, or before if needed.

28  
29 421 The dose-escalation part of the study will terminate once 10 patients have been treated and  
30  
31 422 evaluated at a dose currently identified as the recommended dose. Further patients will then be  
32  
33 423 accrued in the expansion cohort, where toxicity data collected over the first 18-week period and DLT  
34  
35 424 assessment will be analyzed approximately every 10 patients with the possibility of modification of  
36  
37 425 the recommended dose, based on model-based estimates.

38  
39 426 Specifications of the model are detailed in appendix, as well as the results of a simulation study  
40  
41 427 evaluating the operating characteristics of the proposed design.

#### 42 428 PHASE II

43  
44 429 The phase II is based on a one-stage design based on an efficacy endpoint (3-year bRFS). Assuming  
45  
46 430 that information will be available for all patients at 3 years, the endpoint follows a binomial  
47  
48 431 distribution. The design was thus defined considering exact tests, as published by A'Hern [39].  
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3 432 From the literature, the expected bRFS rate at 3 years is approximately 50% in this patient population  
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5 433 with various salvage therapies. A 3-year bRFS equal to or lower than 0.50 is deemed insufficient for  
6  
7 434 further evaluation of this approach [p0=0.50]. The considered alternative hypothesis is p1=0.70].  
8  
9

10 435 The Phase II part of the study will need to include 44 patients (including the patients recruited in the  
11  
12 436 dose-finding part of the phase I, allocated at the dose level finally identified as the recommended  
13  
14 437 dose). If all 44 patients are evaluable at 3 years, the treatment strategy will be considered to be  
15  
16 438 insufficiently effective if  $\leq 27$  patients are alive without a biochemical relapse at 3 years.  
17

18  
19 439 The operating characteristics of the design are:

- 20  
21 440
  - p0=0.50, p1=0.70
- 22  
23 441
  - Defined Type I error = 0.05 (computed type-I error of the design = 0.048)
- 24  
25 442
  - Defined Power = 0.85 (computed power = 0.861)
- 26  
27

28 443 If some patient data are censored before 3 years, the 3-year bRFS will be estimated using Kaplan-  
29  
30 444 Meier method and the lower boundary of the 90% confidence interval will be compared to p0=0.50.  
31  
32 445 The conclusion will be positive if we can reject the null hypothesis p0=0.50 at a one-sided 5% alpha  
33  
34 446 level.  
35

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37 447

#### 38 39 448 PATIENT AND PUBLIC INVOLVEMENT

40  
41 449 Patients were not involved in the idea conception of this trial.

42  
43 450 Patients were not involved in the design of this study nor in recruitment of the study.  
44  
45

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#### 48 49 453 **Discussion**

50  
51 454 To date, no standard local treatment exists for patients with an intraprostatic recurrence after  
52  
53 455 radiotherapy. A number of treatments options exist including: radical prostatectomy, brachytherapy,  
54  
55 456 HIFU, cryotherapy, and more recently SBRT. These treatments are associated with a variety of  
56  
57 457 genitourinary and gastrointestinal toxicities and complications. The literature to date consists mainly  
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3 458 of retrospective and small prospective series making it difficult to assess and compare these  
4  
5 459 techniques. Philippou et al compared oncologic and toxicity outcomes of SRP versus nonsurgical  
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7 460 therapies except SBRT with a meta-regression analysis. Oncologic and toxicity outcomes appear to be  
8  
9  
10 461 similar; however, all nonsurgical salvage modalities may be associated with better continence  
11  
12 462 outcomes [40].

13  
14 463 The sensitivity of PSMA-PET is higher than that of choline-PET for the detection of lymph node  
15  
16 464 disease [41]. Unfortunately PSMA PET is not routinely available in France. A modification of the  
17  
18 465 inclusion criteria is being drafted to allow PSMA PET if this examination becomes available during the  
19  
20  
21 466 study period. To have a high sensitivity, a lymph node staging must be extensive, which can have side  
22  
23 467 effects in this context. Furthermore clinical and biological selection criteria (no high risk cancer  
24  
25 468 before first treatment, PSA level, PSA doubling time,...) are designed to select the patients to have  
26  
27  
28 469 most likely intra-prostatic recurrence only.

29  
30 470 The phase I part of GETUG-AFU 31 trial will evaluate SBRT dose of 30 Gy in 5 fractions, over 12 days,  
31  
32 471 and then depending on tolerance, 36 Gy in 6 fractions over 12 days. The latter, 36 Gy in 6 fractions, is  
33  
34 472 the current scheme used at the Oscar Lambret Centre for all repeat SBRT. This dose is higher than  
35  
36 473 that described by Jereczek-Fossa et al. (30 Gy in 5 fractions) [29], discussed as being too low [30], but  
37  
38  
39 474 lower than the dose used by Fuller (38 Gy in 4 fractions) [30]. A lower dose (5 x 5 Gy) was used in  
40  
41 475 Zerini et al [32]. We have decided to initially use a phase I study, using dose-limiting toxicity criteria,  
42  
43 476 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  
44  
45  
46 477 phase I radiotherapy trials, late complications are often not taken into account and there is currently  
47  
48 478 no consensus on the methodology used for these studies. Although most phase I radiotherapy  
49  
50 479 studies use a 3+3 design, it is not suitable for these studies as it does not assess late toxicity. More  
51  
52 480 complex designs such as the TITE-CRM are recommended, which will shorten the duration of the  
53  
54  
55 481 entire trial and efficiently uses patient information throughout the study [42].

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## 484 Abbreviations

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

497

498

## 499 **Declarations**

500 Ethics approval and consent to participate

501 The study has been submitted and approved by ethics committee (the ethical committee “Ile de  
502 France III” (2017-A00008-45) for all study sites. The study opened in February 2018.

503 A written informed consent will be obtained from the study participants.

504 There is an agreement between each participating center and Unicancer. Each protocol version is  
505 signed by the principal investigator. We have a copy of each signed document.

506 In France, according to the current law, a protocol can be subjected to any regional Ethics  
507 Committee, even if no hospital of this region takes part to the trial. The choice is made according to  
508 the workload of every committee. The opinion of this Ethics Committee applies to all the national  
509 centers.

510

511 Consent for publication

1  
2  
3 512 A signed informed consent is obtained from all patients included in the trial.  
4  
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6 513

7 514 Availability of data and material

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10 515 The data set used and/or analysed during the current study are available from the corresponding  
11  
12 516 author on reasonable request. Not all data are obtained yet since the study is still ongoing.  
13

14 517

15  
16 518 Competing interests

17  
18  
19 519 The authors declare that they have no competing interests.  
20

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22  
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26

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31  
32 525 writing the manuscript.  
33

34 526

35  
36 527 Author contributions

37  
38  
39 528 Study Conception: DP. Revision of study design and protocol: DP, MCLD, ET, LC, MD, SN, ERL. Study  
40  
41 529 coordination: DP, MCLD, ET, SN. All authors read and approved the final manuscript.  
42

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48

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666 **Figures legends**

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

668 Fig 2. Detailed description of study flow chart.

669 (1.Patient will be contacted by phone 14 weeks after starting SBRT to assess toxicity; an additional visit may be scheduled if required; 2

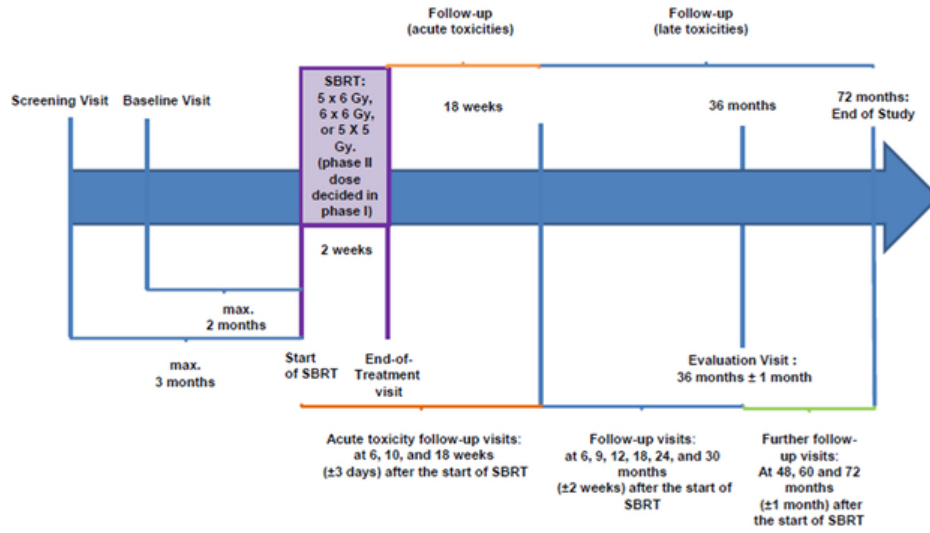
670 .Before inclusion, during regular follow-up and in case of biochemical recurrence after SBRT; 3 .Before inclusion and in case of biochemical

671 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

672 for patients who have consented to participate in the biological ancillary study)

673

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56x32mm (300 x 300 DPI)

Visits	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		
	ScV	BV		W6	W10	W14 <sup>1</sup>	W18	M6	M9	M12	M18	M24	M30	M36	M48	M60	M72/End of Study
Eligibility criteria	X	X															
Signed informed consent form	X	X															
Enrollment in the study		X															
<b>CLINICAL EXAMINATION</b>																	
Weight, height <sup>4</sup> , PS (WHO)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Digital rectal examination (clinical stage)	X	X <sup>5</sup>															
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
<b>QUESTIONNAIRES</b>																	
QLQ-C30 and QLQ-PR25		X					X	X	X	X	X	X	X	X	X	X	X
IPSS		X				X	X	X	X	X	X	X	X	X	X	X	X
IIEF5		X				X	X	X	X	X	X	X	X	X	X	X	X
<b>LABORATORY TESTS</b>																	
CBC, platelets		X															
PT, PTT, and INR		X															
PSA		X				X		X	X	X	X	X	X	X	X	X	X
<b>PATHOLOGICAL EVALUATION</b>																	
Gleason score; number of positive biopsies; total number of biopsies; total length of cancer on biopsies; total length of biopsies	X																
<b>PARACLINICAL INVESTIGATION</b>																	
Multi-parametric MRI (pelvic and prostate)	X <sup>2</sup>						X		X		X		X	X	X	X	X
Choline PET scan	X <sup>3</sup>																
TNM evaluation	X																
<b>TRANSLATIONAL RESEARCH</b>																	
Prostate tumor biopsies (initial before any treatment and at recurrence before SBRT)		X <sup>6</sup>															

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)

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3 **GETUG-AFU 31: a phase I/II multi-center study evaluating the efficacy of repeat stereotactic**  
4 **radiation in patients with intraprostatic tumor recurrence after external radiation therapy.**  
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6 **Appendix: statistical model, simulation study**  
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10 **Statistical considerations**  
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12 A TITE-CRM method with an empiric dose-toxicity model in a Bayesian framework will be used for the  
13 dose-finding part of the trial to identify the recommended dose. The target dose-limiting toxicity  
14 (DLT) probability is set at  $p(\text{DLT})=0.25$ . Three dose levels of SBRT are to be considered: 5 x 5 Gy (DL-  
15 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  
16 explored in case of DLT at the starting dose level. DLTs are evaluated during the 18 weeks following  
17 the initiation of salvage-SBRT. Observations of patients who have no DLT at the time of the analysis  
18 but have not completed the DLT assessment period will be down-weighted in the likelihood,  
19 proportionally to the length of follow up.  
20

21  
22 The Phase I part of the study will include 3 patients at the first dose level. Radiation dose levels for  
23 further patients will be defined based on the estimate of the probability of DLT at each dose-level  
24 considering all available information accumulated so far. Patients will be treated at the best current  
25 estimate of the recommended dose i.e. the dose associated with an estimated probability of DLT the  
26 closest to the target 0.25. Patients may eventually be treated at a dose below the dose  
27 recommended by the model for safety reasons. The patients can be recruited with no minimal time  
28 interval between successive inclusions. Two additional rules will be applied during dose escalation:  
29 no dose skipping and no escalation if at least 1 DLT is observed in the last 3 patients.  
30

31 The dose-escalation part of the study will terminate once 10 patients have been treated and  
32 evaluated at a dose currently identified as the recommended dose. Further patients will then be  
33 accrued in the expansion cohort, where toxicity data collected over the first 18-week period and DLT  
34 assessment will be analyzed approximately every 10 patients with the possibility of modification of  
35 the recommended dose, based on model-based estimates.  
36

37 The Phase II part of the study will need to include 44 patients, including the patients recruited in the  
38 dose-finding part of the phase I allocated at the dose level finally identified as the recommended  
39 dose. Thus, a minimal sample size of 47 patients will be required in this Phase I/II study (in the case  
40 of inclusion of 44 patients at dose level 2 + 3 patients at dose level 1).  
41

42  
43 **Statistical model for dose escalation**  
44

45 A one-parameter empirical power model will be used to assess the relation between the dose level  
46 and the probability of DLT:  $F(d, \alpha) = p_d \exp(\alpha)$  where  $F(d, \alpha)$  is the estimated probability of DLT at dose-  
47 level  $d$ ,  $p_d$  is the prior probability of DLT at dose level  $d$ , and  $\alpha$  is the unknown parameter to be  
48 estimated by the model. The vector  $\{p_{0d}\}$  represent the initial guesses of toxicity probabilities,  
49 reflecting the clinicians' prior belief. The skeleton of initial guesses of toxicity probabilities  $\{p_{0d}\}$   
50 is numerically calibrated using the Lee and Cheung approach (ref ClinTrials 2009) and using the getprior  
51 function of R, ensuring good design's operating characteristics. After discussion with the clinicians,  
52 the delta defining the indifference interval was set at 0.05 ( $p(\text{DLT})=0.25 \pm 0.05$ , i.e. indifference  
53 interval: 0.20 to 0.30) and the prior MTD ( $\text{MTD}_0$ ) at the 2<sup>nd</sup> dose level, meaning that the clinicians  
54 believe, a priori, that the 2<sup>nd</sup> dose (6 x 6 Gy) is probably the MTD. This yields a vector of prior  
55 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  
56 dose level 2 (6 x 6 Gy). The clinicians confirmed that it was in accordance with their initial guesses. A  
57 non-informative prior distribution Normal (0, 1.34) has been assigned for  $\alpha$  in the Bayesian  
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3 computation. The simulation study below confirmed that the operating characteristics and the  
4 behavior of the model defined with these parameters were reasonable.  
5  
6

### 7 **Operating characteristics:**

8  
9 The operating characteristics of the proposed design were evaluated using the R `titesim` function  
10 written by Cheung, and considering six different scenarios:  
11

- 12 - highly toxic,
  - 13 - moderately toxic at dose levels -1 and 1, highly toxic at dose level 2
  - 14 - moderately toxic et every dose level,
  - 15 - similar with prior probabilities,
  - 16 - close to the probabilities but a little less toxic,
  - 17 - little toxic
- 18  
19

20 For the simulation study, we considered that the trial would recruit 47 patients, which is the minimal  
21 sample size required in this Phase I/II study.

22 The following rules were implemented: no dose skipping in escalation, and no escalation if >1 DLT  
23 observed among < 3 patients.

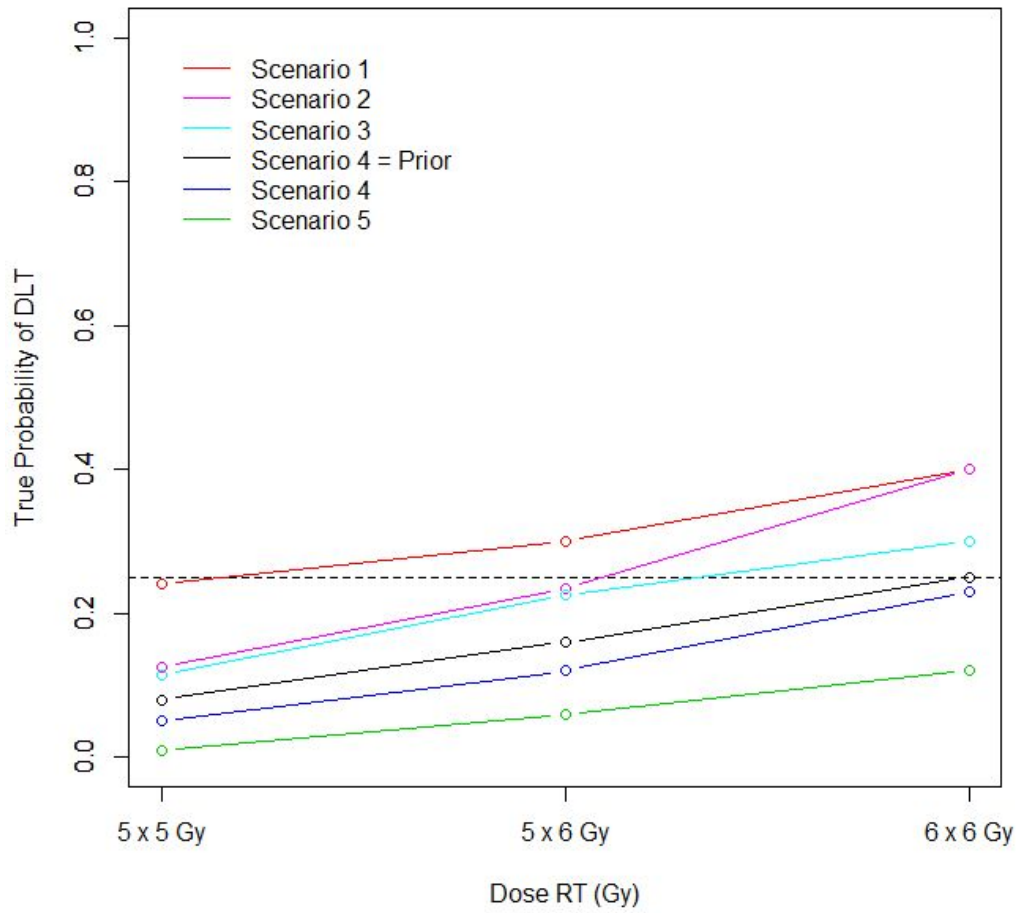
24 For each case, 1000 trials were simulated. The Monte Carlo estimation of the percentage of dose  
25 selection, the average number of patients treated at each dose level, the average number of  
26 observed DLTs at each dose level demonstrated that the modified CRM design can efficiently identify  
27 the MTD, with a reasonable probability of overdosing, and expose few patients to toxicity.

28 A second set of simulations was performed considering a sample size of 13 patients, which is the  
29 minimal expected recruitment in the Phase I part of the study. As expected, the performance is much  
30 better when the reassessment is continued during the expansion phase (Phase II part). This is one of  
31 the advantages of the CRM method.  
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### 34 **Figure 1: Scenarios studied**

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**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	Item No	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <a href="#">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)</a>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <a href="#">ClinicalTrials : NCT03438552</a>
	2b	All items from the World Health Organization Trial Registration Data Set <a href="#">IdRCB : 2017-A00008-45</a>
Protocol version	3	Date and version identifier <a href="#">version n°3.0 – 26/08/2016</a>
Funding	4	Sources and types of financial material, and other support  <a href="#">Support by a grant of National Institute of Cancer (INCA)</a>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <a href="#">Docteur David PASQUIER</a> <a href="#">Centre Oscar Lambret - Département de Radiothérapie</a> <a href="#">3, rue Frédéric Combemale - BP307 59020 Lille Cedex</a> <a href="#">Tél : 03.20.29.59.11 - Fax : 03.20.29.58.96</a> <a href="#">E-mail : <u>d-pasquier@o-lambret.fr</u></a>
	5b	Name and contact information for the trial sponsor <b>UNICANCER</b> <a href="#">101 Rue de Tolbiac, 75654 Paris</a> <a href="#">Soazig NENAN +33 (0)185 343 113</a> <a href="mailto:s-nenan@unicancer.fr">s-nenan@unicancer.fr</a> <a href="#">Meryem BRIHOUM +33 (0)1 80 50 12 95</a> <a href="mailto:m-brihoum@unicancer.fr">m-brihoum@unicancer.fr</a>

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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

1 Trial design 8 Description of trial design including type of trial (eg, parallel group,  
2 crossover, factorial, single group), allocation ratio, and framework (eg,  
3 superiority, equivalence, noninferiority, exploratory)  
4 Study Type: Interventional ; phase I/II  
5 Primary Purpose: Treatment  
6 Intervention Model: Sequential Assignment  
7 Masking: Open Label  
8 Endpoint Classification: Safety/Efficacy Study  
9 Enrollment: 47  
10

### 11 **Methods: Participants, interventions, and outcomes**

12  
13 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and  
14 list of countries where data will be collected. Reference to where list of  
15 study sites can be obtained  
16 Centers are hospitals and clinics (see below) :  
17  
18 Centre François Baclesse, Caen, France  
19 Principal Investigator: Marlon SILVA  
20  
21 Centre Jean Perrin, Clermont-Ferrand, France  
22 Principal Investigator: Geneviève LOOS  
23  
24 Centre George François Leclerc, Dijon, France  
25 Principal Investigator: Gilles CREHANGE  
26  
27 Centre Oscar Lambret, Lille, France  
28 Principal Investigator: David PASQUIER  
29  
30 Centre Léon Bérard, Lyon, France  
31 Principal Investigator: Pascal Pommier  
32  
33 Institut régional du Cancer de Montpellier, Montpellier, France  
34 Principal Investigator: David AZRIA  
35  
36 Groupe Hospitalier Pitié-Salpêtrière, Paris, France  
37 Principal Investigator: Philippe MAINGON  
38  
39 ICO -Site René Gauducheau, Saint-Herblain, France  
40 Principal Investigator: Stephane SUPLOT  
41  
42 Institut de Cancérologie Lucien Neuwirth, Saint-Priest-en-Jarez, France  
43 Principal Investigator: Nicolas MAGNE  
44  
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Eligibility criteria      10	<p>Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)</p> <p>Minimum Age: 18 Years Gender: Male Accepts Healthy Volunteers?: No</p> <p><b>Inclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1. Biochemical recurrence occurring at least 2 years after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL)</li> <li>2. T1-T2c and PSA <math>\leq</math>20 ng/mL and Gleason score <math>\leq</math>7 at initial diagnosis of prostate cancer before the initial/first treatment.</li> <li>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.</li> <li>4. Clinical stage T1-T2 on relapse; unilateral extracapsular extension (T3a) on MRI permitted except posteriorly relative to the rectum</li> <li>5. Estimated clinical target volume (CTV) / prostate volume <math>&lt;</math> 0.5 based on imaging and biopsies</li> <li>6. Pelvic and prostatic assessment by multiparametric MRI- Absence of pelvic or metastatic recurrence proven by choline PET scan</li> <li>7. Performance status WHO 0-1</li> <li>8. PSA level <math>\leq</math>10 ng/mL at baseline (before salvage-SBRT)</li> <li>9. PSA doubling time <math>&gt;</math>10 months</li> <li>10. International Prostate Cancer Score (IPSS) <math>\leq</math>12</li> <li>11. Uroflowmetry with a maximum flow rate <math>&gt;</math>10 mL/s, a postvoid residual urine volume <math>&lt;</math>150 mL, and a urine volume <math>&gt;</math>150 mL.</li> <li>12. No other anti-cancer treatment since the external radiotherapy administered as first-line treatment</li> <li>13. No other anti-cancer treatment planned for the current recurrence</li> <li>14. No contraindication to fiducial marker implants; haemostatic disorders must be corrected before implantation</li> <li>15. Age <math>&gt;</math>18 years</li> <li>16. Life-expectancy greater than or equal to 5 years (Lee scale)</li> <li>17. Patient registered with a health insurance system</li> <li>18. Patient who has signed the informed consent form</li> <li>19. Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests, and other study procedures indicated in the protocol.</li> </ol> <p><b>Exclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1. Lymph node or metastatic spread</li> <li>2. Late post-radiotherapy urinary or gastrointestinal toxicity of grade <math>\geq</math>2 (following primary radiotherapy)</li> <li>3. Other cancers in the last 5 years except for non-melanoma-type skin cancer</li> <li>4. History of inflammatory bowel disease</li> <li>5. Anticoagulant treatment</li> <li>6. Contraindications to undergoing MRI</li> <li>7. Prostate volume <math>&gt;</math>80 cc</li> <li>8. Transurethral resection of the prostate (TURP) in the 6 months before registrations</li> <li>9. Presence of rectal telangiectasia grade 3 classified by the Vienne Rectoscopy Score (obligatory rectoscopy)</li> <li>10. Previous rectal surgery</li> <li>11. Patients unable to undergo medical follow-up in the study for geographical, social or psychological</li> <li>12. Person deprived of their liberty or under protective custody or guardianship</li> <li>13. Patients enrolled in another therapeutic study</li> </ol> <p>All patients during the SBRT planning with a ratio of clinical target volume (CTV) / prostate volume <math>&gt;</math> 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.</p>
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2	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
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4			
5			Focal salvage SBRT (5x6 Gy, 6x6 Gy, 5x5 Gy)
6		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
7			Not applicable
8			
9			
10		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
11			Not applicable
12			
13		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
14			
15			
16			Anticoagulant treatment
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22	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
23			<b>Primary Outcome Measure:</b>
24			[ 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.
25			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.
26			
27			[ Time Frame: 6 years ] Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate
28			
29			<b>Secondary Outcome Measure:</b>
30			1. Time Frame: 3 years]
31			Evaluation of acute and late genitourinary toxicities of the salvage-SBRT
32			2. [Time Frame: 6 years]
33			Estimate the efficacy of the salvage-SBRT in terms of clinical progression-free survival and overall survival
34			3. [Time Frame: 6 years]
35			Evaluation of Quality of life after salvage-SBRT
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49	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)
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22	Sample size	14	<p>Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations</p> <p>47 patients</p> <p><b>Sample Size Calculations:</b> 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 <math>p_1=0.70</math>, with a test against <math>p_0=0.50</math> at a one-sided 5%-alpha level.</p>
23 24 25 26	Recruitment	15	<p>Strategies for achieving adequate participant enrolment to reach target sample size</p> <p><a href="#">Communication and follow-up of the participating centers</a></p>

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

31 32 33 34 35 36 37 38	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
39 40 41 42	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
43 44 45 46	Implementation	16c	Who will generate the allocation sequence: who will enrol participants: and who will assign participants to interventions:
47 48 49 50 51 52 53 54 55 56 57 58 59 60	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how <a href="#">Not applicable</a>
		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial <a href="#">Not applicable</a>

## 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 <a href="#">Describe in protocol and data management procedures</a>
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) <a href="#">Not applicable</a>
	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) <a href="#">Not applicable</a>

## 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 <a href="#">Coordinator : validate the risk analysis (LIR) and the monitoring plan</a> <a href="#">Project Manager : determine the risk analysis (LIR) and write the monitoring plan</a> <a href="#">Clinical Research Associate (CRA) :perform monitoring according the monitoring plan</a>
	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

1			
2	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
3			spontaneously reported adverse events and other unintended effects of trial
4			interventions or trial conduct
5			<a href="#">This point is provided by the vigilance unit of the sponsor. All details are described</a>
6			<a href="#">in the protocol</a>
7			
8	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the
9			process will be independent from investigators and the sponsor
10			<a href="#">Actually and according the risk analysis, no audit is planned</a>
11			
12	<b>Ethics and dissemination</b>		
13			
14	Research ethics	24	Plans for seeking research ethics committee/institutional review board
15	approval		(REC/IRB) approval
16			<a href="#">N° IdRCB : 2017-A00008-45</a>
17			
18			<a href="#">Initial Approval by CPP Nord-Ouest I (Committee for the Protection of</a>
19			<a href="#">Personnes/Ethic committee) : 25/07/2017</a>
20			<a href="#">Approval Number: CPP3517-I</a>
21			
22	Protocol	25	Plans for communicating important protocol modifications (eg, changes to
23	amendments		eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators,
24			REC/IRBs, trial participants, trial registries, journals, regulators)
25			<a href="#">Each major protocol amendment is submitted to authorities for approval.</a>
26			<a href="#">After approval, it is communicated to all the actors of this project (investigators,</a>
27			<a href="#">trial centers, trial registry ...)</a>
28			
29	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants
30			or authorised surrogates, and how (see Item 32)
31			<a href="#">Principal Investigator or sub-investigator</a>
32			
33		26b	Additional consent provisions for collection and use of participant data and
34			biological specimens in ancillary studies, if applicable
35			<a href="#">Not applicable</a>
36			
37	Confidentiality	27	How personal information about potential and enrolled participants will be
38			collected, shared, and maintained in order to protect confidentiality before,
39			during, and after the trial
40			<a href="#">Collected by investigators and CRA on each trial centers. These data are</a>
41			<a href="#">anonymized.</a>
42			<a href="#">Shared on the eCRF.</a>
43			<a href="#">There is a control access on the eCRF</a>
44			
45			
46	Declaration of	28	Financial and other competing interests for principal investigators for the
47	interests		overall trial and each study site
48			<a href="#">None</a>
49			
50	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure
51			of contractual agreements that limit such access for investigators
52			<a href="#">Directly on the eCRF</a>
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2	Ancillary and post-	30	Provisions, if any, for ancillary and post-trial care, and for compensation to
3	trial care		those who suffer harm from trial participation
4			<a href="#">Not applicable</a>
5			
6	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
7	policy		participants, healthcare professionals, the public, and other relevant groups
8			(eg, via publication, reporting in results databases, or other data sharing
9			arrangements), including any publication restrictions
10			
11			A publication is planned; no publication restriction.
12			
13		31b	Authorship eligibility guidelines and any intended use of professional writers
14			
15			Coordinator will be the first author; co investigators will be authors.
16			
17			
18			
19		31c	Plans, if any, for granting public access to the full protocol, participant-level
20			dataset, and statistical code
21			
22			N/A
23			
24	<b>Appendices</b>		
25			
26	Informed consent	32	Model consent form and other related documentation given to participants
27	materials		and authorised surrogates
28			
29			
30	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
31	specimens		specimens for genetic or molecular analysis in the current trial and for future
32			use in ancillary studies, if applicable
33			
34			<a href="#">Not applicable</a>

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\*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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026666.R2
Article Type:	Protocol
Date Submitted by the Author:	22-May-2019
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<b>Primary Subject Heading</b>:	Oncology
Secondary Subject Heading:	Urology
Keywords:	prostate cancer, stereotactic body radiation therapy, recurrent prostate cancer, salvage radiotherapy

SCHOLARONE™  
Manuscripts

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3 1 **GETUG-AFU 31: a phase I/II multi-center study evaluating the safety and efficacy of salvage**  
4  
5 2 **stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation**  
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7 3 **therapy; study protocol**  
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8 29  
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10 30 Word count : 5193  
11  
12 31  
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## 14 32 **ARTICLE SUMMARY**

15  
16 33 Introduction. Prostate cancer is the third most important cancer in terms of mortality in men. No  
17  
18 34 standard local treatment exists for patients with an intraprostatic recurrence after radiotherapy.  
19  
20 35 Stereotatic body radiotherapy (SBRT) could be a curative treatment for local recurrence.  
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22

23 36 Methods and Analysis. We plan to perform a multicenter prospective phase I/II study including at  
24  
25 37 least 47 patients. Eligible patients are patients with biochemical recurrence occurring at least 2 years  
26  
27 38 after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2  
28  
29 39 ng/mL):  
30

31  
32 40 T1–T2c and PSA  $\leq 20$  ng/mL and Gleason score  $\leq 7$  at initial diagnosis before the initial/first  
33  
34 41 treatment;

35  
36 42 Recurrence of prostatic adenocarcinoma proven by histology following radiotherapy by  
37  
38 43 transrectal or transperineal sextant biopsies of the two lobes of the prostate, with a minimum of  
39  
40 44 12 biopsies, irrespective of Gleason score;

41  
42 45 Clinical stage T1-T2 on relapse;

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44 46 Pelvic and prostatic assessment by multiparametric MRI;

45  
46 47 Absence of pelvic or metastatic recurrence proven by choline or PSMA PET scan;

47  
48 48 PSA level  $\leq 10$  ng/mL at baseline (before salvage-SBRT), PSA doubling time  $> 10$  months, IPSS  $\leq 12$ .  
49

50  
51 49 The phase I primary objective is the selection of the recommended dose for salvage-SBRT (5 x 6 Gy, 6  
52  
53 50 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity. The dose of salvage-SBRT will be selected using a  
54  
55 51 Time-to-Event Continual-Reassessment-Method based on dose-limiting toxicity defined as grade  $\geq 3$   
56  
57 52 gastrointestinal or urinary toxicity or any other grade 4 adverse event. The phase II primary objective  
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3 53 is to estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate.

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5 54 Phase II secondary objectives are: acute and late toxicities, quality of life, clinical progression free  
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7 55 survival and overall survival.

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10 56 Ethics and Dissemination. The study has received ethical approval from the Ethics committee "Ile-de-  
11  
12 57 France III". Academic dissemination will occur through publication and conference presentations.

13  
14 58 **Trial registration:** NCT03438552

15  
16 59 **Date of trial registration:** November 14, 2017

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20  
21 61 **Strengths and limitations of this study funding**

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23 62 - Very innovative trial evaluating stereotactic body radiotherapy for recurrent prostate cancer,  
24  
25 63 the only ongoing trial of this kind to our knowledge

26  
27 64 - Clinical trial supported by the GETUG-AFU cooperative group, expert in the field, and funded  
28  
29 65 by the French National Cancer Institute (INCa)

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31 66 - Time-to-Event Continual Reassessment Method, a more appropriate method than the 3+3  
32  
33 67 design to quantify late toxicity in phase I radiotherapy trials

34  
35 68 - Proof-of-concept study; therefore, further research will be required

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41 70 **Keywords:** prostate cancer, stereotactic body radiation therapy, recurrent prostate cancer

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## 74 **Background**

75 Prostate cancer is the third most important cancer in terms of mortality in men (after lung and  
76 colorectal cancer), and the fourth leading cancer overall [1]. In the European Union, it was predicted  
77 that 72600 patients would die from prostate cancer in 2015. The rate of recurrence/relapse of  
78 prostate cancer after primary external beam radiotherapy varies from 21% to 65% depending on the  
79 study [2,3]. Zelefsky et al. performed biopsies on 339 patients after treatment with 3-dimensional  
80 conformal radiotherapy (3D-CRT) or intensity modulated RT for T1c-T3 stage prostate cancer, with a  
81 minimum follow-up of 2.5 years [2]. They found that the rate of positive biopsy according to  
82 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  
83 years biopsy was performed in 312/843 patients included in MRC RT01 trial. A positive biopsy was  
84 prognostic of worse biological progression free survival compared with negative and suspicious  
85 biopsies, hazard ratio (HR)=4.81 (95% confidence interval [CI]: 2.50-9.26, p<0.001). The estimate for  
86 survival was HR=1.58 (95% CI: 0.52-4.78, p=0.42).

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

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

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2  
3 100 specific mortality rate of 36% vs. 6% ( $p=0.0001$ ). Thus late relapse and long PSA doubling time are  
4  
5 101 prognostic factors of solely intraprostatic relapse.

6  
7 102 Prostate-specific antigen (PSA) is a validated biomarker for prostate cancer. PSA levels are  
8  
9 103 extensively used to monitor response to radical prostatectomy (RP) and external-beam radiotherapy  
10 104 (EBRT). The serum PSA level is an important surrogate for recurrence in prostate cancer patients. The  
11  
12 105 recommendations of the Radiation Therapy Oncology Group (RTOG) ASTRO Phoenix Consensus  
13  
14 106 Conference suggested that an increase of  $\geq 2$  ng/mL from the nadir be used to define  
15  
16 107 recurrence/relapse [6]. It is important to note that biochemical recurrence may indicate local or  
17  
18 108 systemic disease recurrence, and may require prostate biopsy for confirmation particularly when  
19  
20 109 local salvage treatments are being considered [7].

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22  
23 110 A number of different salvage treatments have been used after failure of primary radiotherapy.  
24  
25 111 RP is more invasive than brachytherapy, ultrasound, high-intensity focused ultrasound (HIFU), and  
26  
27 112 SBRT. Below is a brief discussion of the results obtained with each techniques and its associated  
28  
29 113 toxicity and complications.

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32 114 Salvage RP (SRP) is a treatment option after local recurrence following EBRT. However, the  
33  
34 115 morbidity, including incontinence and erectile dysfunction, is higher than that observed with first-line  
35  
36 116 RP patients. A systematic literature review [7] reported that the probability of biochemical relapse–  
37  
38 117 free survival (bRFS) following SRP in prostate cancer patients was 47-82% after 5 years and 28-53%  
39  
40 118 after 10 years. SRP has an increased risk of adverse events due to fibrosis and poor wound healing  
41  
42 119 after radiotherapy. Furthermore, SRP after radiotherapy compared to primary RP has a significantly  
43  
44 120 higher rate of urinary and gastrointestinal morbidity [8]. The review above [7], reported that the  
45  
46 121 most frequent complications were anastomotic stricture (7-41%) and rectal injury (0-28%). The  
47  
48 122 majority (50-91%) of men had erectile dysfunction before SRP and 80-100% after surgery. Post-  
49  
50 123 operative urinary continence ranged from 21-90%.

51  
52 124 In a recent review, salvage brachytherapy after EBRT is reported to achieve biochemical control  
53  
54 125 rates of 20% to 89% (median follow-up: 19 to 108 months) [9]. Rates of genitourinary toxicities range  
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3 126 from 12% to 87% for grade 1-2, and 3% to 47% for grade 3-4 toxicities. Similarly, the rates of  
4  
5 127 gastrointestinal toxicities range from 4% to 65% for grade 1-2, and 0% to 20% for grade 3-4 toxicities.  
6  
7 128 Erectile dysfunction was observed in 2% to 95% of men. A phase II study of salvage high-dose-rate  
8  
9 129 brachytherapy (HDR) for treating recurrent prostate cancer after definitive external beam  
10  
11 130 radiotherapy was reported by Yamada [10]. The 42 patients enrolled, with biopsy proven recurrence,  
12  
13 131 were treated with salvage HDR (iridium-192) with a resulting bRFS at 5 years of 68.5% (median  
14  
15 132 follow-up of 36 months [range: 2-66 months]). Acute genitourinary toxicity was observed: grade 1,  
16  
17 133 38% of patients and grade 2: 40%. Similarly, late genitourinary toxicity was observed: grade 1, 38% of  
18  
19 134 patients and grade 2, 48%. In addition, 1 patient had a grade 3 urinary incontinence and 3 had grade  
20  
21 135 3 urethral strictures. Late gastrointestinal toxicities were observed: grade 1, 43% of patients and  
22  
23 136 grade 2, 14%. More recently, a study of 83 prostate cancer patients with local recurrence after  
24  
25 137 radiotherapy treated with high-dose-rate brachytherapy was reported [11]. The 3-year and 5-year  
26  
27 138 bRFS were 76% and 67%. A phase II study of the RTOG in 100 patients was recently presented: twelve  
28  
29 139 (14%) experienced late grade 3 genitourinary/gastrointestinal adverse effects. This rate of late grade  
30  
31 140 3 toxicity (14%) was not unacceptable by the predetermined protocol specification, without any  
32  
33 141 grade 4-5 events. The only factor predictive of late toxicity was implant dose, underlining the need  
34  
35 142 for meticulous planning and technique to limit the final delivered dose [12]. In France, a phase II  
36  
37 143 study, "Brachytherapy for Recurrent Prostate Cancer" (CAPRICUR) was recently completed [13].  
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43 144 HIFU is another less invasive salvage treatments following recurrence. HIFU uses focused  
44  
45 145 ultrasound to generate heat (85°C) which induces tissue necrosis [14]. The following studies have  
46  
47 146 investigated the use of salvage-HIFU after initial radiotherapy. A French group treated 290 men with  
48  
49 147 biopsy-confirmed recurrent prostate cancer, after radiotherapy, with salvage HIFU [15]. At 7 years,  
50  
51 148 the cancer-specific survival rate was 80% and the metastasis-free survival rate was 79.6%. Recto-  
52  
53 149 urethral fistula occurred in 0.4% of patients and 19.5% had grade 2/3 incontinence. Half of the  
54  
55 150 patients also received hormone therapy. Survival without relapse at 5 years after HIFU, by D'Amico  
56  
57 151 risk groups prior to their initial treatment, was 45% (favorable), 31% (intermediate risk) and 21%  
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3 152 (high risk). In this cohort, the grade  $\leq 3$  urinary incontinence levels were 23% (favorable), 14%  
4  
5 153 (intermediate risk) and 9% (high risk). Nearly 8% of patients required an artificial sphincter following  
6  
7 154 HIFU. Importantly, pubic osteitis occurred in 2.5% of patients despite adherence to parameters  
8  
9 155 specific to HIFU following radiotherapy [15].

11  
12 156 Cryotherapy is thermo-ablative treatment; the third-generation argon/helium-based cryotherapy  
13  
14 157 system creates precise isotherms through ultrathin needles [16]. In a retrospective multicenter series  
15  
16 158 pooling 279 patients, survival without biochemical relapse at 5 years was 54%. Prostatic biopsies  
17  
18 159 showed tumor persistence in 32% of patients following cryotherapy [17]. In a paired case-controlled  
19  
20 160 study, prostatectomy and cryotherapy were compared following radiotherapy. Survival without  
21  
22 161 relapse (PSA nadir + 0.4 ng/mL) at 5 years was significantly lower after cryotherapy (21% vs. 61%,  
23  
24 162  $p < 0.001$ ); this was confirmed by the 5-year OS rate of 85%, cryotherapy, vs 95%, radical  
25  
26 163 prostatectomy ( $p = 0.001$ ) [18]. Intermediate results from a study investigating third-generation  
27  
28 164 cryotherapy as a salvage treatment of locally recurrent prostate cancer after radiotherapy was  
29  
30 165 published [19]. The 5-year bRFS rate (Phoenix definition) was 43.5% and with a 5-year OS rate of  
31  
32 166 92.3%. Mild complications (grades 1 and 2) were reported including: mild incontinence (9.4%), acute  
33  
34 167 rectal pain (31.3%), lower urinary tract symptoms (15.6%) and erectile dysfunction (57.1%). Grade 3  
35  
36 168 toxicities: incontinence (3.1%) and urethral sloughing (3.1%) were observed.

37  
38  
39 169 Androgen-deprivation therapy (ADT) alone (continuous or intermittent) is commonly given to  
40  
41 170 patients with biochemical relapse after radiotherapy [20]. In a series based on data from a North  
42  
43 171 American national registry (CaPSURE), 71% of patients were treated for biochemical relapse after  
44  
45 172 prostatectomy or radiotherapy. ADT was initiated in 93% of these patients, and the remaining  
46  
47 173 patients were treated with surgery, brachytherapy, cryotherapy, or repeat external radiotherapy  
48  
49 174 [21]. ADT may cause adverse effects impacting patient's quality of life (including: hot flushes, erectile  
50  
51 175 dysfunction and reduced libido, cognitive impairment, and anemia). The metabolic changes  
52  
53 176 associated with hormone therapy may also increase the risk of cardiovascular morbidity. The  
54  
55 177 reduction in bone mass is maximal in the first year and increases with the duration of castration; the  
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3 178 risk of fracture is increased in patients surviving for more than 5 years [22-23]. The guidelines suggest  
4  
5 179 that a simple follow-up can be implemented for local recurrence in patients with a limited life  
6  
7 180 expectancy or for those who do not wish to undergo local salvage treatment. The last European  
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10 181 Association of Urology guidelines [24] recommended to perform salvage surgery in experienced  
11  
12 182 centres due to the increased rate of side effects. It is recommended to offer/discuss HIFU,  
13  
14 183 cryosurgical ablation and salvage brachytherapy to/with patients without evidence of metastasis and  
15  
16 184 with histologically proven local recurrence and to inform patients about the experimental nature of  
17  
18  
19 185 these approaches. The level of evidence for each of these recommendations is 3 [24].

20  
21 186 SBRT delivers highly conformal, high-dose radiation in a few fractions (hypofractionation), typically  
22  
23 187 5 to 7 fractions for prostate cancer. It is reported that tissues with a low  $\alpha/\beta$  ratio, as for prostate  
24  
25 188 cancer, are more sensitive to large doses of radiation per fraction. The surrounding normal tissue  
26  
27 189 could have similar or higher  $\alpha/\beta$  ratio. This suggests that hypofractionation (large radiation dose per  
28  
29 190 fraction) may result in improved tumor control with limited toxicity. A pooled analysis of 1100  
30  
31  
32 191 patients included in separate prospective phase II studies in 8 institutions was performed to evaluate  
33  
34 192 the effectiveness of SBRT as a first-line treatment for localized prostate cancer [25]. The SBRT was  
35  
36 193 delivered by CyberKnife with a median dose of 36.25 Gy in 4-5 fractions. The 5-year bRFS rate was  
37  
38 194 93% for all patients. Thus relapse-free survival rates after SBRT compare favourably with other  
39  
40 195 definitive treatments for low and intermediate-risk patients with a short follow up. SBRT is well  
41  
42 196 tolerated with a low effect on quality of life [25-28]. In addition sexual function appeared to be  
43  
44 197 spared in the majority of patients [25-28].

45  
46  
47 198 SBRT has also been used as a salvage treatment following failure of external radiotherapy.  
48  
49 199 Jereczek-Fossa et al. published data on 34 consecutive patients treated with robotic SBRT for isolated  
50  
51 200 recurrent primary, lymph node, or metastatic prostate cancer [29]. Of the 34 patients, 15 patients  
52  
53 201 had intraprostatic recurrence, confirmed by biopsy, and were treated with SBRT (CyberKnife) with a  
54  
55 202 median dose of 30 Gy in 5 fractions. Fourteen patients showed a biochemical response; the median  
56  
57 203 survival without recurrence was 13 months. Five patients presented a clinical relapse, including one  
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3 204 new intraprostatic recurrence. Urinary toxicity was low, with a grade 3 urinary toxicity in only one  
4  
5 205 patient. No case of acute or late gastrointestinal toxicity was reported. This good gastrointestinal  
6  
7 206 tolerability has subsequently been confirmed [29-32]. In Fuller et al twenty-nine patients were  
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9  
10 207 treated in a phase II trial with stereotactic radiotherapy for intraprostatic recurrence [30]. Eligible  
11  
12 208 patients had to present biopsy-proven intraprostatic recurrence graded T1 to T3N0M0 more than 2  
13  
14 209 years post-radiotherapy and without a pre-existing grade >1 radiotherapy toxicity. The prior median  
15  
16 210 dose delivered was 73.8 Gy and the median interval between the treatments was 88 months. The  
17  
18 211 dose delivered to the entire gland was 34 Gy in five fractions over 5 days (heterogeneous  
19  
20 212 intraprostatic dose of up to 50 Gy). With a median follow-up of 24 months, survival without  
21  
22 213 recurrence was 82%. Toxicity was acceptable, with 18% grade  $\geq 2$  urinary toxicity, including one  
23  
24 214 patient with a grade 4 toxicity, and no late gastrointestinal toxicity above grade 1. Particular  
25  
26 215 attention should be given to patients who still exhibit urinary toxicity after initial radiotherapy [30].  
27  
28 216 Our preliminary retrospective results in 23 patients treated for this indication were published  
29  
30 217 recently [31]. A total dose of 36 Gy was prescribed in 6 fractions of 6 Gy. Nineteen patients had a  
31  
32 218 whole-gland and four a partial treatment. Median follow-up was 23 months (range 6 to 40 months).  
33  
34 219 We observed no grade 4 or 5 toxicity. Two patients presented grade 3 toxicities. Others toxicities  
35  
36 220 include urinary (5 grade 2 and 9 grade 1) and rectal toxicities (2 grade 2 and 2 grade 1). The dose  
37  
38 221 levels selected in our study are close to those used in de novo patients, and the same as those  
39  
40 222 described in retrospective salvage treatment series. These schemes seem to provide an acceptable  
41  
42 223 compromise between efficacy and toxicity but have not been evaluated prospectively.  
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48 224 To date, no standard local treatment exists for patients with an intraprostatic recurrence after  
49  
50 225 radiotherapy [33]. A number of treatments options exist including: radical prostatectomy,  
51  
52 226 brachytherapy, HIFU, cryotherapy, and stereotactic radiotherapy. The literature to date consists  
53  
54 227 mainly of retrospective and small prospective series making it difficult to assess and compare these  
55  
56 228 techniques. In recent years, SBRT has been used to treat localized prostate cancer in the primary  
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58 229 setting but also as a salvage treatment after failure of radiotherapy. The initial results of these  
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3 230 retrospective studies are promising, with respect to survival and tolerance, but further studies are  
4  
5 231 required to confirm these initial results. Our proposed study will provide further evidence of SBRT as  
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7 232 a supplementary non-invasive curative treatment for local recurrence following radiotherapy. This  
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9 233 study could provide the foundation for prospective studies comparing the available salvage  
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11 234 treatments after radiotherapy.  
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### 16 236 **Methods/design**

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19 237 This study is approved by the Ethics committee "Ile de France III" (2017-A00008-45) and is registered  
20  
21 238 on clinicaltrials.gov (NCT03438552). This multicenter open-labelled phase I/II study will initially select  
22  
23 239 the SBRT scheme (phase I), either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy. The effectiveness of SBRT scheme  
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25 240 selected in phase I will then be evaluated in a single-arm multicenter phase II study.

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28 241 PHASE I primary objective and assessment:

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30 242 Selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on  
31  
32 243 dose-limiting toxicity observed during the 18 weeks following the initiation of salvage-SBRT. The dose  
33  
34 244 of salvage-SBRT will be selected using a Time-to-Event Continual Reassessment Method [34-36]  
35  
36 245 based on dose-limiting toxicity defined as grade  $\geq 3$  gastrointestinal or urinary toxicity or any other  
37  
38 246 grade 4 adverse event observed during the 18 weeks following the initiation of salvage-SBRT.

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40  
41 247 PHASE II primary objective and assessment:

42  
43 248 Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate (Phoenix  
44  
45 249 definition: increase in serum total PSA  $\geq 2$  ng/mL above the nadir). Time to biochemical relapse-free  
46  
47 250 survival will be computed from registration. Patients alive without biochemical progression at the  
48  
49 251 time of the analysis will be censored at the last follow-up date. In the event of death, whatever the  
50  
51 252 cause of death, the patient will be considered as a failure.

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54 253 PHASE II secondary objective(s) and assessment:  
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56 254  
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3 256      ○ Acute and late genitourinary and gastrointestinal toxicities over the first 3 years according to  
4  
5 257      the NCI-CTCAE V4.03 classification (June 14th, 2010), International prostate Symptom Score  
6  
7 258      (IPSS) score for urinary symptoms, and International Index of Erectile Function (IIEF5) for  
8  
9  
10 259      erectile function. Patients will be followed for 5 years after salvage SBRT to assess late  
11  
12 260      toxicity. Patients with second biochemical recurrence will not be excluded in order to assess  
13  
14 261      late toxicity.
- 15  
16 262      ○ Quality of life will be evaluated based on the EORTC QLQ-C30 and QLQ-PR25 scales. The Time  
17  
18 263      Until Definitive Deterioration (TUDD) will be computed from registration until the first  
19  
20 264      observation of a definitive deterioration of the quality of life, defined as a score decreased by  
21  
22 265      10 points (in the case of global health scale and functional scales) or increased by 10 points  
23  
24 266      (in the case of symptom scales) compared to the score at baseline, without later  
25  
26 267      improvement superior to 10 points compared to baseline score.
- 27  
28 268      ○ Clinical progression-free survival is defined as the time interval between the date of  
29  
30 269      registration and the date of clinical progression (local progression assessed by the physical  
31  
32 270      examination, or appearance of metastatic lesions) or death irrespective of the cause.
- 33  
34 271      ○ Overall survival is defined as the time interval between the date of registration and the date  
35  
36 272      of death irrespective of the cause.
- 37  
38 273      ○ Erythroblast transformation-specific related gene (ERG) fusion expression will be evaluated  
39  
40 274      using immunohistochemistry (IHC) tests. ERG fusion and androgen-receptor splice variant 7  
41  
42 275      (ARV7) expression will be evaluated on biopsies before the first radiotherapy treatment (at  
43  
44 276      diagnosis, if available) and before salvage radiotherapy after biochemical recurrence.
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52 278      **DIAGNOSIS AND INCLUSION CRITERIA:**

- 53  
54 279      ○ Biochemical recurrence occurring at least 2 years after external radiotherapy  
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56 280      for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2  
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58 281      ng/mL)
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- T1–T2c and PSA  $\leq 20$  ng/mL and Gleason score  $\leq 7$  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  $\leq 10$  ng/mL at baseline (before salvage-SBRT)
  - PSA doubling time  $> 10$  months
  - IPSS  $\leq 12$
  - 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

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3 308 ○ Life-expectancy greater than or equal to 5 years (Lee scale)  
4  
5 309 ○ Patient registered with a health insurance system  
6  
7 310 ○ Patient who has signed the informed consent form  
8  
9  
10 311 ○ Patients willing and able to comply with the scheduled visits, treatment plan,  
11  
12 312 laboratory tests, and other study procedures indicated in the protocol.  
13

14 313 EXCLUSION CRITERIA:

- 15  
16 314 ○ Lymph node or metastatic spread  
17  
18 315 ○ Late post-radiotherapy urinary or gastrointestinal toxicity of grade  $\geq 2$   
19  
20 316 (following primary radiotherapy)  
21  
22  
23 317 ○ Other cancers in the last 5 years except for non-melanoma-type skin cancer  
24  
25 318 ○ History of inflammatory bowel disease  
26  
27 319 ○ Anticoagulant treatment  
28  
29  
30 320 ○ Contraindications to undergoing MRI  
31  
32 321 ○ Prostate volume > 80 cc  
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34 322 ○ Transurethral resection of the prostate (TURP) in the 6 months before  
35  
36 323 registration  
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39 324 ○ Presence of rectal telangiectasia grade 3 classified by the Vienne Rectoscopy  
40  
41 325 Score (obligatory rectoscopy) [37,38]  
42  
43 326 ○ Previous rectal surgery  
44  
45 327 ○ Patients unable to undergo medical follow-up in the study for geographical,  
46  
47 328 social or psychological  
48  
49  
50 329 ○ Person deprived of their liberty or under protective  
51

52 330 INTERVENTION

53  
54 331 A flow chart presenting the different steps from inclusion until treatment is presented in Fig. 1.  
55  
56 332 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  
57  
58 333 delivered over a maximum of 12 days to provide a total dose of 25 to 36 Gy. This radiotherapy may  
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3 334 be administered with the CyberKnife® or a linear accelerator allowing stereotactic radiotherapy. The  
4  
5 335 patient will be placed in a stable and reproducible supine position. Intraprostatic markers (fiducials)  
6  
7 336 will be implanted before the dosimetric CT-scan and MRI are performed. The choice of markers is left  
8  
9  
10 337 to the discretion of each participating site (gold seeds, etc.). The site needs to ensure that the  
11  
12 338 repositioning of the prostate is precise ( $\leq 2$  mm), allowing an exact overlay between dosimetric MRI  
13  
14 339 and computed tomography (CT)-scan. The implant of fiducials is obligatory irrespective of the  
15  
16 340 stereotactic radiotherapy technique used. The fiducials can be implanted during or after the biopsies.  
17  
18 341 The CT-scans and MRIs registration is guided by the fiducials. Each team can choose the fiducials  
19  
20 342 visible on the MRI they wish to use and/or integrate a specific sequence during the centering MRI for  
21  
22 343 better visualization.

23  
24  
25 344 An mpMRI and CT-scan will be carried out at least one week after fiducial implantation. CT-scan  
26  
27 345 images should be acquired with the patient in the treatment position using the chosen immobilizing  
28  
29 346 system, if required according to centers' standard procedures. An intravenous injection of a contrast  
30  
31 347 product should be administered unless contraindicated. Acquisition should allow anatomical  
32  
33 348 structures and markers (already implanted in the prostate) to be visualized. The bladder will be half-  
34  
35 349 filled (neither full nor empty, i.e. a final voiding 90 minutes before the CT-scan followed by ingestion  
36  
37 350 of 250-350 mL of water). The rectum will be empty and not distended. If necessary rectal enema can  
38  
39 351 be used before CT-scan acquisition. Contiguous CT-scan slices  $\leq 2$  mm thick will be taken between the  
40  
41 352 L5-S1 joint space and the small trochanters. After image transfer to a planimetric console, fiducial-  
42  
43 353 based registration with the prostatic mpMRI will take place in order to provide a better definition of  
44  
45 354 the Gross Target Volume (GTV) and prostatic contours, especially the apex. Fiducial-based CT-MRI  
46  
47 355 registration is mandatory. Multimodality image registration with Choline PET is possible but not  
48  
49 356 mandatory.

50  
51  
52 357 Delineation of the target volume will be carried out by a radiotherapist experienced in the  
53  
54 358 definition of prostate volumes on CT-scans and MRIs. The mpMRI-defined contour will be integrated  
55  
56 359 with the CT-scan derived contours in order to define tumor and the prostatic apex more precisely.  
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3 360 GTV will be represented by lesion defined on the multiparametric MRI +/- choline PET; a 5-7 mm  
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5 361 margin around the GTV will be used to define the Clinical Target Volume (CTV). CTV is contained in  
6  
7 362 the prostate, except in the case of extracapsular extension (unilateral extracapsular extension on MRI  
8  
9 363 permitted except posteriorly relative to the rectum). In the case where the positive biopsy(ies) are  
10  
11 364 outside and adjacent to the visible lesions on the MRI, the zone containing these biopsies must be  
12  
13 365 included in the CTV so that the prostate cancer recurrence not visible on the MRI is included in the  
14  
15 366 CTV. If no lesion is visible on the MRI and/or choline PET, the zone containing positive biopsies must  
16  
17 367 be included in the CTV. For example: MRI +/-choline PET lesion in 3p and 4p according to ESUR  
18  
19 368 guidelines, with positive biopsies in 1p, 3p and 4p: CTV = MRI GTV + 5 mm + the posterior right base.  
20  
21 369 The total CTV should not be more than half of the total volume of the prostate by MRI. The planning  
22  
23 370 target volume (PTV) will be obtained by an expansion of 2 mm around the CTV in this repeat  
24  
25 371 radiotherapy context. This margin involves that the probability of coverage at 25, 30, or 36 Gy is low,  
26  
27 372 so the reporting will include D2%, 50%, D98% and D95% to describe as much as possible delivered  
28  
29 373 dose. Organs at risk constraints are specified in Table 1. Daily image guided radiation therapy is  
30  
31 374 mandatory, intra fraction tracking is recommended.  
32  
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37 375

Rectum	Bladder	Urethra + 3 mm
V27 Gy <2 cc	V27 Gy <5 cc	V24 Gy <30%
V12 Gy <20%	V12 Gy <15%	D <sub>max</sub> (35 mm <sup>3</sup> ) <39 Gy
		V36 Gy <1 cc

376

377 Table 1. Organs at risk constraints

378

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

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3 383 which will be centralized in order to verify that the constraints are being observed. For each site, the  
4  
5 384 dosimetric data will be subject to a centralized review prior to SBRT administration in order to verify  
6  
7 385 that constraints are being observed. Follow-up visits are described in Figures 1 and 2.  
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10 386

#### 11 387 SAMPLE SIZE CALCULATION

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13  
14 388 Required number of patients to be included: minimum 47 patients. The total sample size will depend  
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16 389 upon the number of patients allocated at the different dose levels in the dose-finding parts of the  
17  
18 390 trial. A minimum of 13 patients will be recruited before the expansion phase is open (Phase II part). A  
19  
20 391 total of 44 patients allocated at the recommended dose (recruited in the dose-escalation stage or in  
21  
22 392 the expansion phase) and evaluable at 3 years are required for the main analysis of the Phase II part  
23  
24 393 of the trial to ensure an 85%-power if 3-year bRFS is  $p_1=0.70$ , with a test against  $p_0=0.50$  at a one-  
25  
26 394 sided 5%-alpha level.  
27  
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30 395

#### 31 396 STATISTICAL CONSIDERATIONS

##### 32 397 PHASE I

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35 398 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  
36  
37 399 level is 5 x 6 Gy. The lower dose level, 5 x 5 Gy, will be considered if excessive toxicity is reported at  
38  
39 400 the first dose-level (5 x 6 Gy). A TimeTo Event-Continuous Reassessment Method (TITE-CRM) with an  
40  
41 401 empiric dose-toxicity model in a Bayesian framework will be used for the dose-finding part of the trial  
42  
43 402 to identify the recommended dose. The target dose limiting toxicity (DLT) probability is set at  
44  
45 403  $p(\text{DLT})=0.25$ . Observations of patients who have no DLT at the time of the analysis but have not  
46  
47 404 completed the DLT assessment period will be down-weighted in the likelihood, proportionally to the  
48  
49 405 length of follow up; for instance, if the last patient has been recruited 8 weeks before a new patient  
50  
51 406 is available for enrolment, and is evaluated at week 10 with no DLT, then his observation is attributed  
52  
53 407 a weight of  $10/18=0.56$ .  
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3 408 At least three patients will be enrolled at the first dose-level and fully evaluated over the 18-week  
4  
5 409 study period before the dose is escalated to the next dose-level. Radiation dose levels for further  
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7 410 patients will be defined based on the estimate of the probability of DLT at each dose-level  
8  
9 411 considering all available information accumulated so far. Patients will be treated at the best current  
10  
11 412 estimate of the recommended dose i.e. the dose associated with an estimated probability of DLT the  
12  
13 413 closest to the target 0.25. Patients may eventually be treated at a dose below the dose  
14  
15 414 recommended by the model for safety reasons. The patients can be recruited with no minimal time  
16  
17 415 interval between successive inclusions. During the dose-escalation part of the trial, safety data will  
18  
19 416 have to be reported in the data base in real time. A monthly teleconference meeting with the  
20  
21 417 participation of the biostatistician, the trial coordinator and a representative of the sponsor, to  
22  
23 418 summarize toxicity observations and define the dose to be allocated to the next patient(s) will be  
24  
25 419 held. Safety data will be discussed with an Independent Data Monitoring Committee (IDMC) at the  
26  
27 420 end of the dose-escalation part of trial, or before if needed.

31  
32 421 The dose-escalation part of the study will terminate once 10 patients have been treated and  
33  
34 422 evaluated at a dose currently identified as the recommended dose. Further patients will then be  
35  
36 423 accrued in the expansion cohort, where toxicity data collected over the first 18-week period and DLT  
37  
38 424 assessment will be analyzed approximately every 10 patients with the possibility of modification of  
39  
40 425 the recommended dose, based on model-based estimates.

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42 426 Specifications of the model are detailed in appendix, as well as the results of a simulation study  
43  
44 427 evaluating the operating characteristics of the proposed design.

#### 47 428 PHASE II

48  
49 429 The phase II is based on a one-stage design based on an efficacy endpoint (3-year bRFS). Assuming  
50  
51 430 that information will be available for all patients at 3 years, the endpoint follows a binomial  
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53 431 distribution. The design was thus defined considering exact tests, as published by A'Hern [39].  
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3 432 From the literature, the expected bRFS rate at 3 years is approximately 50% in this patient population  
4  
5 433 with various salvage therapies. A 3-year bRFS equal to or lower than 0.50 is deemed insufficient for  
6  
7 434 further evaluation of this approach [p0=0.50]. The considered alternative hypothesis is p1=0.70].  
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9

10 435 The Phase II part of the study will need to include 44 patients (including the patients recruited in the  
11  
12 436 dose-finding part of the phase I, allocated at the dose level finally identified as the recommended  
13  
14 437 dose). If all 44 patients are evaluable at 3 years, the treatment strategy will be considered to be  
15  
16 438 insufficiently effective if  $\leq 27$  patients are alive without a biochemical relapse at 3 years.  
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18  
19 439 The operating characteristics of the design are:

- 20  
21 440
  - p0=0.50, p1=0.70
- 22  
23 441
  - Defined Type I error = 0.05 (computed type-I error of the design = 0.048)
- 24  
25 442
  - Defined Power = 0.85 (computed power = 0.861)
- 26  
27

28 443 If some patient data are censored before 3 years, the 3-year bRFS will be estimated using Kaplan-  
29  
30 444 Meier method and the lower boundary of the 90% confidence interval will be compared to p0=0.50.  
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32 445 The conclusion will be positive if we can reject the null hypothesis p0=0.50 at a one-sided 5% alpha  
33  
34 446 level.  
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#### 38 39 448 PATIENT AND PUBLIC INVOLVEMENT

40  
41 449 Patients were not involved in the idea conception of this trial.

42  
43 450 Patients were not involved in the design of this study nor in recruitment of the study.  
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#### 48 49 453 **Discussion**

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51 454 To date, no standard local treatment exists for patients with an intraprostatic recurrence after  
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53 455 radiotherapy. A number of treatments options exist including: radical prostatectomy, brachytherapy,  
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55 456 HIFU, cryotherapy, and more recently SBRT. These treatments are associated with a variety of  
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57 457 genitourinary and gastrointestinal toxicities and complications. The literature to date consists mainly  
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3 458 of retrospective and small prospective series making it difficult to assess and compare these  
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5 459 techniques. Philippou et al compared oncologic and toxicity outcomes of SRP versus nonsurgical  
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7 460 therapies except SBRT with a meta-regression analysis. Oncologic and toxicity outcomes appear to be  
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10 461 similar; however, all nonsurgical salvage modalities may be associated with better continence  
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12 462 outcomes [40].

13  
14 463 The sensitivity of PSMA-PET is higher than that of choline-PET for the detection of lymph node  
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16 464 disease [41]. Unfortunately PSMA PET is not routinely available in France. A modification of the  
17  
18 465 inclusion criteria is being drafted to allow PSMA PET if this examination becomes available during the  
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20 466 study period. To have a high sensitivity, a lymph node staging must be extensive, which can have side  
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23 467 effects in this context. Furthermore clinical and biological selection criteria (no high risk cancer  
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25 468 before first treatment, PSA level, PSA doubling time,...) are designed to select the patients to have  
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27 469 most likely intra-prostatic recurrence only.

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29  
30 470 The phase I part of GETUG-AFU 31 trial will evaluate SBRT dose of 30 Gy in 5 fractions, over 12 days,  
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32 471 and then depending on tolerance, 36 Gy in 6 fractions over 12 days. The latter, 36 Gy in 6 fractions, is  
33  
34 472 the current scheme used at the Oscar Lambret Centre for all repeat SBRT. This dose is higher than  
35  
36 473 that described by Jereczek-Fossa et al. (30 Gy in 5 fractions) [29], discussed as being too low [30], but  
37  
38 474 lower than the dose used by Fuller (38 Gy in 4 fractions) [30]. A lower dose (5 x 5 Gy) was used in  
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40 475 Zerini et al [32]. We have decided to initially use a phase I study, using dose-limiting toxicity criteria,  
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42 476 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  
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44 477 phase I radiotherapy trials, late complications are often not taken into account and there is currently  
45  
46 478 no consensus on the methodology used for these studies. Although most phase I radiotherapy  
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48 479 studies use a 3+3 design, it is not suitable for these studies as it does not assess late toxicity. More  
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50 480 complex designs such as the TITE-CRM are recommended, which will shorten the duration of the  
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52 481 entire trial and efficiently uses patient information throughout the study [42].  
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## 484 Abbreviations

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

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498

## 499 **Declarations**

500 Ethics approval and consent to participate

501 The study has been submitted and approved by ethics committee (the ethical committee “Ile de  
502 France III” (2017-A00008-45) for all study sites. The study opened in February 2018.

503 A written informed consent will be obtained from the study participants.

504 There is an agreement between each participating center and Unicancer. Each protocol version is  
505 signed by the principal investigator. We have a copy of each signed document.

506 In France, according to the current law, a protocol can be subjected to any regional Ethics  
507 Committee, even if no hospital of this region takes part to the trial. The choice is made according to  
508 the workload of every committee. The opinion of this Ethics Committee applies to all the national  
509 centers.

510

511 Consent for publication

1  
2  
3 512 A signed informed consent is obtained from all patients included in the trial.  
4

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7 514 Availability of data and material

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10 515 The data set used and/or analysed during the current study are available from the corresponding  
11  
12 516 author on reasonable request. Not all data are obtained yet since the study is still ongoing.

13  
14 517

15  
16 518 Competing interests

17  
18 519 None declared.

19  
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21 520

22  
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28  
29 524 body had no role in the design of the study, collection, analysis, and interpretation of data and in  
30  
31 525 writing the manuscript.

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34 526

35  
36 527 Author contributions

37  
38 528 Study Conception: DP. Revision of study design and protocol: DP, MCLD, ET, LC, MD, SN, ERL. Study  
39  
40 529 coordination: DP, MCLD, ET, SN. All authors read and approved the final manuscript.

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666 **Figures legends**

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

668 Fig 2. Detailed description of study flow chart.

669 (1.Patient will be contacted by phone 14 weeks after starting SBRT to assess toxicity; an additional visit may be scheduled if required; 2

670 .Before inclusion, during regular follow-up and in case of biochemical recurrence after SBRT; 3 .Before inclusion and in case of biochemical

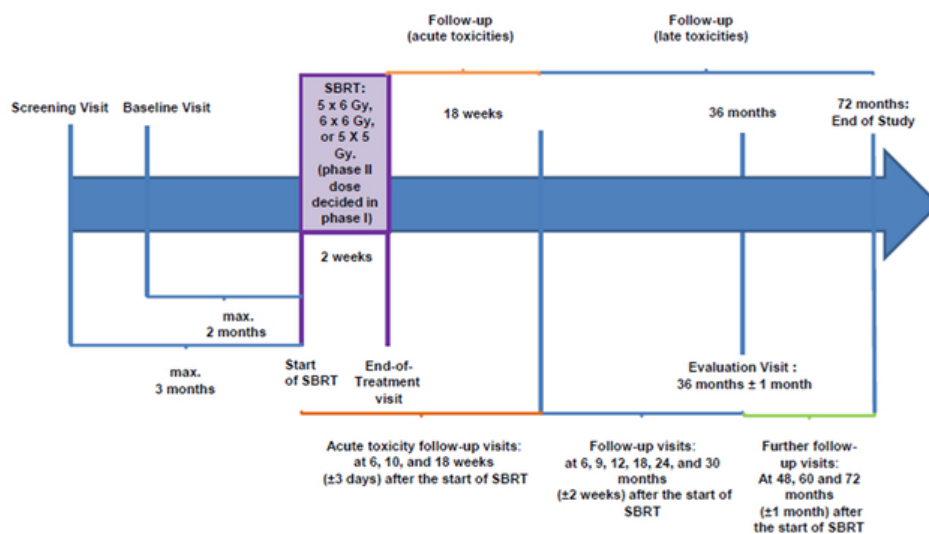
671 recurrence after SBRT; 4.Patient's height will only be measured at the screening visit; 5. If not done at the screening visit.; 6.Only applicable

672 for patients who have consented to participate in the biological ancillary study)

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For peer review only





56x32mm (300 x 300 DPI)

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Visits	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		
	ScV	BV		W6	W10	W14 <sup>1</sup>	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															
<b>CLINICAL EXAMINATION</b>																	
Weight, height <sup>4</sup> , PS (WHO)	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X
Digital rectal examination (clinical stage)	X	X <sup>5</sup>				X		X	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
<b>QUESTIONNAIRES</b>																	
QLQ-C30 and QLQ-PR25		X					X		X	X	X	X	X	X	X	X	X
IPSS		X				X	X		X	X	X	X	X	X	X	X	X
IIIEF5		X				X	X		X	X	X	X	X	X	X	X	X
<b>LABORATORY TESTS</b>																	
CBC, platelets		X															
PT, PTT, and INR		X															
PSA		X				X		X	X	X	X	X	X	X	X	X	X
<b>PATHOLOGICAL EVALUATION</b>																	
Gleason score; number of positive biopsies; total number of biopsies; total length of cancer on biopsies; total length of biopsies	X																
<b>PARACLINICAL INVESTIGATION</b>																	
Multi-parametric MRI (pelvic and prostate)	X <sup>2</sup>							X		X		X		X	X	X	X
Choline PET scan	X <sup>3</sup>																
TNM evaluation	X																
<b>TRANSLATIONAL RESEARCH</b>																	
Prostate tumor biopsies (initial before any treatment and at recurrence before SBRT)		X <sup>6</sup>															

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)

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3 **GETUG-AFU 31: a phase I/II multi-center study evaluating the efficacy of repeat stereotactic**  
4 **radiation in patients with intraprostatic tumor recurrence after external radiation therapy.**  
5  
6

7 **Appendix: statistical model, simulation study**  
8  
9

10 **Statistical considerations**  
11

12 A TITE-CRM method with an empiric dose-toxicity model in a Bayesian framework will be used for the  
13 dose-finding part of the trial to identify the recommended dose. The target dose-limiting toxicity  
14 (DLT) probability is set at  $p(\text{DLT})=0.25$ . Three dose levels of SBRT are to be considered: 5 x 5 Gy (DL-  
15 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  
16 explored in case of DLT at the starting dose level. DLTs are evaluated during the 18 weeks following  
17 the initiation of salvage-SBRT. Observations of patients who have no DLT at the time of the analysis  
18 but have not completed the DLT assessment period will be down-weighted in the likelihood,  
19 proportionally to the length of follow up.  
20

21  
22 The Phase I part of the study will include 3 patients at the first dose level. Radiation dose levels for  
23 further patients will be defined based on the estimate of the probability of DLT at each dose-level  
24 considering all available information accumulated so far. Patients will be treated at the best current  
25 estimate of the recommended dose i.e. the dose associated with an estimated probability of DLT the  
26 closest to the target 0.25. Patients may eventually be treated at a dose below the dose  
27 recommended by the model for safety reasons. The patients can be recruited with no minimal time  
28 interval between successive inclusions. Two additional rules will be applied during dose escalation:  
29 no dose skipping and no escalation if at least 1 DLT is observed in the last 3 patients.  
30

31 The dose-escalation part of the study will terminate once 10 patients have been treated and  
32 evaluated at a dose currently identified as the recommended dose. Further patients will then be  
33 accrued in the expansion cohort, where toxicity data collected over the first 18-week period and DLT  
34 assessment will be analyzed approximately every 10 patients with the possibility of modification of  
35 the recommended dose, based on model-based estimates.  
36

37 The Phase II part of the study will need to include 44 patients, including the patients recruited in the  
38 dose-finding part of the phase I allocated at the dose level finally identified as the recommended  
39 dose. Thus, a minimal sample size of 47 patients will be required in this Phase I/II study (in the case  
40 of inclusion of 44 patients at dose level 2 + 3 patients at dose level 1).  
41  
42

43 **Statistical model for dose escalation**  
44

45 A one-parameter empirical power model will be used to assess the relation between the dose level  
46 and the probability of DLT:  $F(d, \alpha) = p_d^{exp(\alpha)}$  where  $F(d, \alpha)$  is the estimated probability of DLT at dose-  
47 level  $d$ ,  $p_d$  is the prior probability of DLT at dose level  $d$ , and  $\alpha$  is the unknown parameter to be  
48 estimated by the model. The vector  $\{p_{od}\}$  represent the initial guesses of toxicity probabilities,  
49 reflecting the clinicians' prior belief. The skeleton of initial guesses of toxicity probabilities  $\{p_{od}\}$  is  
50 numerically calibrated using the Lee and Cheung approach (ref ClinTrials 2009) and using the getprior  
51 function of R, ensuring good design's operating characteristics. After discussion with the clinicians,  
52 the delta defining the indifference interval was set at 0.05 ( $p(\text{DLT})=0.25 \pm 0.05$ , i.e. indifference  
53 interval: 0.20 to 0.30) and the prior MTD ( $\text{MTD}_0$ ) at the 2<sup>nd</sup> dose level, meaning that the clinicians  
54 believe, a priori, that the 2<sup>nd</sup> dose (6 x 6 Gy) is probably the MTD. This yields a vector of prior  
55 probabilities  $\{p_{ok}\}$  equal to 0.08, 0.16 and 0.25 for dose level -1 (5 x 5Gy), dose level 1 (5 x 6 Gy) and  
56 dose level 2 (6 x 6 Gy). The clinicians confirmed that it was in accordance with their initial guesses. A  
57 non-informative prior distribution Normal (0, 1.34) has been assigned for  $\alpha$  in the Bayesian  
58  
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3 computation. The simulation study below confirmed that the operating characteristics and the  
4 behavior of the model defined with these parameters were reasonable.  
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8 **Operating characteristics:**  
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10 The operating characteristics of the proposed design were evaluated using the R `titesim` function  
11 written by Cheung, and considering six different scenarios:

- 12 - highly toxic,  
13 - moderately toxic at dose levels -1 and 1, highly toxic at dose level 2  
14 - moderately toxic at every dose level,  
15 - similar with prior probabilities,  
16 - close to the probabilities but a little less toxic,  
17 - little toxic  
18

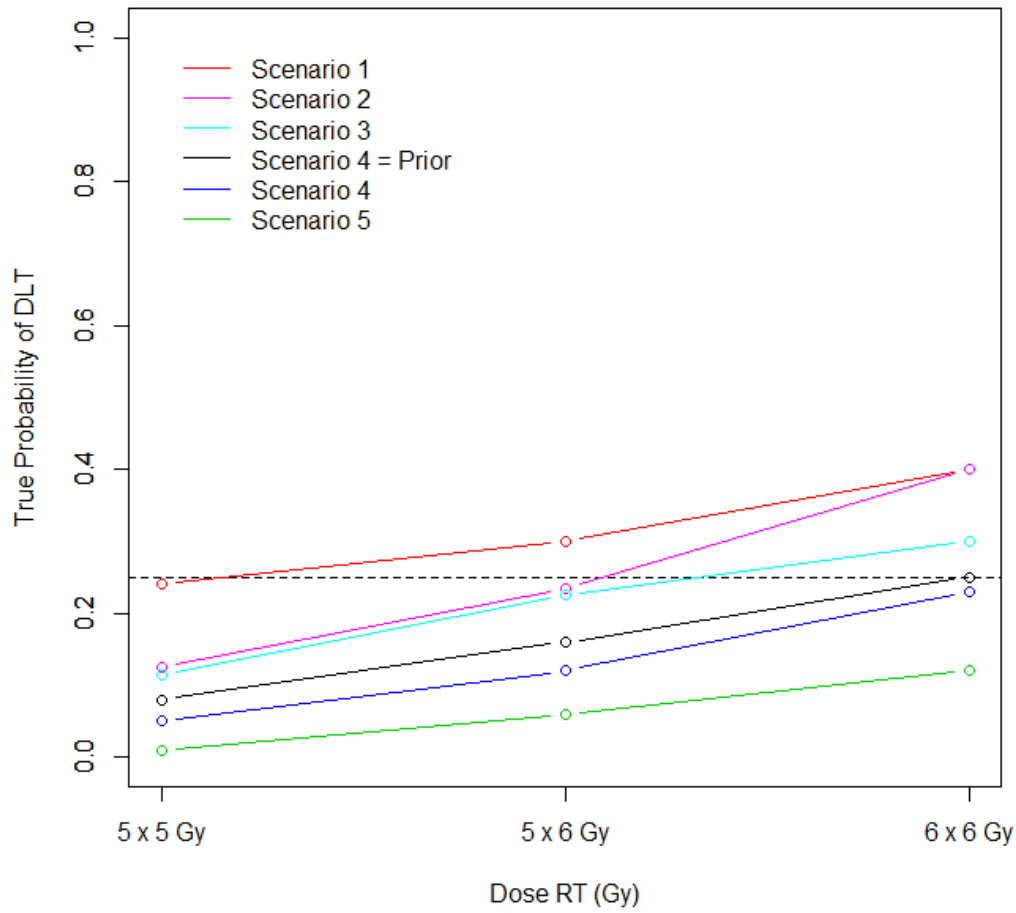
19  
20 For the simulation study, we considered that the trial would recruit 47 patients, which is the minimal  
21 sample size required in this Phase I/II study.

22 The following rules were implemented: no dose skipping in escalation, and no escalation if >1 DLT  
23 observed among < 3 patients.

24 For each case, 1000 trials were simulated. The Monte Carlo estimation of the percentage of dose  
25 selection, the average number of patients treated at each dose level, the average number of  
26 observed DLTs at each dose level demonstrated that the modified CRM design can efficiently identify  
27 the MTD, with a reasonable probability of overdosing, and expose few patients to toxicity.  
28

29 A second set of simulations was performed considering a sample size of 13 patients, which is the  
30 minimal expected recruitment in the Phase I part of the study. As expected, the performance is much  
31 better when the reassessment is continued during the expansion phase (Phase II part). This is one of  
32 the advantages of the CRM method.  
33

34 **Figure 1: Scenarios studied**  
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Review only

**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
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <a href="#">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)</a>	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <a href="#">ClinicalTrials : NCT03438552</a>	2
	2b	All items from the World Health Organization Trial Registration Data Set <a href="#">IdRCB : 2017-A00008-45</a>	2
Protocol version	3	Date and version identifier <a href="#">version n°2.0 06/10/2017</a>	1
Funding	4	Sources and types of financial material, and other support <a href="#">Support by a grant of National Institute of Cancer (INCA)</a>	Not explicitly mentioned in the protocol
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <a href="#">Docteur David PASQUIER</a> <a href="#">Centre Oscar Lambret - Département de Radiothérapie</a> <a href="#">3, rue Frédéric Combemale - BP307 59020 Lille Cedex</a> <a href="#">Tél : 03.20.29.59.11 - Fax : 03.20.29.58.96</a> <a href="#">E-mail : d-pasquier@o-lambret.fr</a>	2



1			
2	5b	Name and contact information for the trial sponsor	1-2
3		<b>UNICANCER</b>	
4		101 Rue de Tolbiac, 75654 Paris	
5		Soazig NENAN +33 (0)185 343 113 s-	
6		nenan@unicancer.fr	
7		Meryem BRIHOUM +33 (0)1 80 50 12 95 m-	
8		brihoum@unicancer.fr	
9			
10			
11	5c	Role of study sponsor and funders, if any, in study	46; 49
12		design; collection, management, analysis, and	
13		interpretation of data; writing of the report; and the	
14		decision to submit the report for publication, including	
15		whether they will have ultimate authority over any of	
16		these activities	
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21	5d	Composition, roles, and responsibilities of the	42-44; 46
22		coordinating centre, steering committee, endpoint	
23		adjudication committee, data management team, and	
24		other individuals or groups overseeing the trial, if	
25		applicable (see Item 21a for data monitoring	
26		committee)	
27			
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31	<b>Introduction</b>		
32			
33	Background and	6a	Description of research question and justification for
34	rationale		undertaking the trial, including summary of relevant
35			studies (published and unpublished) examining
36			benefits and harms for each intervention
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40		6b	Explanation for choice of comparators
41			Not
42			applicable
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2	Objectives	7	Specific objectives or hypotheses	22-23
3			<b>Primary objective :</b>	
4				
5			Selection of the recommended dose for salvage-SBRT	
6			(either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on dose-	
7			limiting toxicity observed during the 18 weeks following the	
8			initiation of salvage-SBRT.	
9				
10				
11			Estimate the efficacy of the salvage-SBRT in terms of	
12			biochemical relapse-free survival rate	
13				
14			<b>Secondary objectives</b>	
15			Evaluation of acute and late genitourinary toxicities of the	
16			salvage-SBRT	
17				
18			Estimate the efficacy of the salvage-SBRT in terms of	
19			clinical progression-free survival and overall survival	
20				
21			Evaluation of Quality of life after salvage-SBRT	
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24				
25	Trial design	8	Description of trial design including type of trial (eg,	4
26			parallel group, crossover, factorial, single group),	
27			allocation ratio, and framework (eg, superiority,	
28			equivalence, noninferiority, exploratory)	
29			Study Type: Interventional	
30			Primary Purpose: Treatment	
31			Intervention Model: Sequential Assignment	
32			Number of Arms: 3	
33			Masking: Open Label	
34			Endpoint Classification: Safety/Efficacy Study	
35			Enrollment: 47	
36				
37				

**Methods: Participants, interventions, and outcomes**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Study setting	9	<p>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</p> <p>Centers are hospitals and clinics (see below) :</p> <p>Centre François Baclesse, Caen, France Principal Investigator: Marlon SILVA</p> <p>Centre Jean Perrin, Clermont-Ferrand, France Principal Investigator: Geneviève LOOS</p> <p>Centre George François Leclerc, Dijon, France Principal Investigator: Gilles CREHANGE</p> <p>Centre Oscar Lambret, Lille, France Principal Investigator: David PASQUIER</p> <p>Centre Léon Bérard, Lyon, France Principal Investigator: Pascal Pommier</p> <p>Institut régional du Cancer de Montpellier, Montpellier, France Principal Investigator: David AZRIA</p> <p>Groupe Hospitalier Pitié-Salpêtrière, Paris, France Principal Investigator: Philippe MAINGON</p> <p>ICO -Site René Gauducheau, Saint-Herblain, France Principal Investigator: Stephane SUPLOT</p> <p>Institut de Cancérologie Lucien Neuwirth, Saint-Priest-en-Jarez, France Principal Investigator: Nicolas MAGNE</p>	<p>Additional form (not in the protocol)</p>
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Eligibility criteria      10	<p>Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)</p> <p>Minimum Age: 18 Years Gender: Male Accepts Healthy Volunteers?: No</p> <p><b>Inclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1. Biochemical recurrence occurring at least 2 years after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL)</li> <li>2. T1-T2c and PSA <math>\leq</math>20 ng/mL and Gleason score <math>\leq</math>7 at initial diagnosis of prostate cancer before the initial/first treatment.</li> <li>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.</li> <li>4. Clinical stage T1-T2 on relapse; unilateral extracapsular extension (T3a) on MRI permitted except posteriorly relative to the rectum</li> <li>5. Estimated clinical target volume (CTV) / prostate volume &lt; 0.5 based on imaging and biopsies</li> <li>6. Pelvic and prostatic assessment by multiparametric MRI- Absence of pelvic or metastatic recurrence proven by choline PET scan</li> <li>7. Performance status WHO 0-1</li> <li>8. PSA level <math>\leq</math>10 ng/mL at baseline (before salvage-SBRT)</li> <li>9. PSA doubling time &gt;10 months</li> <li>10. International Prostate Cancer Score (IPSS) <math>\leq</math>12</li> <li>11. Uroflowmetry with a maximum flow rate &gt;10 mL/s, a postvoid residual urine volume &lt;150 mL, and a urine volume &gt;150 mL.</li> <li>12. No other anti-cancer treatment since the external radiotherapy administered as first-line treatment</li> <li>13. No other anti-cancer treatment planned for the current recurrence</li> <li>14. No contraindication to fiducial marker implants; haemostatic disorders must be corrected before implantation</li> <li>15. Age &gt;18 years</li> <li>16. Life-expectancy greater than or equal to 5 years (Lee scale)</li> <li>17. Patient registered with a health insurance system</li> <li>18. Patient who has signed the informed consent form</li> <li>19. Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests, and other study procedures indicated in the protocol.</li> </ol> <p><b>Exclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1. Lymph node or metastatic spread</li> <li>2. Late post-radiotherapy urinary or gastrointestinal toxicity of grade <math>\geq</math>2 (following primary radiotherapy)</li> <li>3. Other cancers in the last 5 years except for non-melanoma-type skin cancer</li> <li>4. History of inflammatory bowel disease</li> <li>5. Anticoagulant treatment</li> <li>6. Contraindications to undergoing MRI</li> <li>7. Prostate volume &gt;80 cc</li> <li>8. Transurethral resection of the prostate (TURP) in the 6 months before registrations</li> <li>9. Presence of rectal telangiectasia grade 3 classified by the Vienna Rectoscopy Score (obligatory rectoscopy)</li> <li>10. Previous rectal surgery</li> <li>11. Patients unable to undergo medical follow-up in the study for geographical, social or psychological</li> <li>12. Person deprived of their liberty or under protective custody or guardianship</li> </ol>	26-27
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2	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 28-30
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7		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) 31
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12			Not applicable
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14		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) 31
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17			Not applicable
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20		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial 31
21			
22			Concomitant treatment permitted : any treatment considered necessary for the health of the patient
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25	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 23-24
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34			<b>Primary Outcome Measure:</b>
35			[ 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.
36			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.
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43			[ Time Frame: 6 years ] Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate
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47			<b>Secondary Outcome Measure:</b>
48			1. Time Frame: 3 years]
49			Evaluation of acute and late genitourinary toxicities of the salvage-SBRT
50			
51			2. [Time Frame: 6 years]
52			Estimate the efficacy of the salvage-SBRT in terms of clinical progression-free survival and overall survival
53			
54			3. [Time Frame: 6 years]
55			Evaluation of Quality of life after salvage-SBRT
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2	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
3				
4				
5				
6				
7				
8	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	39-40
9			<a href="#">At least 47 patients</a>	
10			<b>Sample Size Calculations</b>	
11				
12				
13				
14				
15				
16				
17				
18	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	44; 50
19			<a href="#">Communication and follow-up of the participating centers</a>	
20				
21				
22				
23	<b>Methods: Assignment of interventions (for controlled trials)</b>			
24	Allocation:			
25				
26	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	25; 39-40
27			<a href="#">TITE-CRM</a>	
28				
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36				
37	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	25
38			<a href="#">Number of inclusion attributed directly by eCRF</a>	
39				
40				
41				
42				
43				
44	Implementation	16c	Who will generate the allocation sequence: <a href="#">computer/eCRF by inclusion program. Biostatistician</a>	25
45			who will enrol participants: <a href="#">Investigator.</a>	
46			and who will assign participants to interventions: <a href="#">Biostatistician.</a>	
47				
48				
49				
50				
51	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Not applicable
52			<a href="#">Not applicable</a>	
53				
54				
55				
56				
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59				
60				

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
		<a href="#">Not applicable</a>	

## 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	30; 31-35; 43-44
		<a href="#">Describe in protocol and data management procedures</a>	
	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	31; 31-35
		<a href="#">Describe in protocol and data management procedures</a>	
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	30; 43-44
		<a href="#">Describe in protocol and data management procedures</a>	
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)	41-42
		<a href="#">Not applicable</a>	
	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)	41-42
		<a href="#">Not applicable</a>	

## Methods: Monitoring

1				
2	Data monitoring	21a	Composition of data monitoring committee (DMC);	42
3			summary of its role and reporting structure; statement	
4			of whether it is independent from the sponsor and	
5			competing interests; and reference to where further	
6			details about its charter can be found, if not in the	
7			protocol. Alternatively, an explanation of why a DMC	
8			is not needed	
9				
10			<a href="#">Coordinator : validate the risk analysis (LIR) and the</a>	
11			<a href="#">monitoring plan</a>	
12				
13			<a href="#">Project Manager : determine the risk analysis (LIR) and</a>	
14			<a href="#">write the monitoring plan</a>	
15				
16			<a href="#">Clinical Research Associate (CRA) :perform monitoring</a>	
17			<a href="#">according the monitoring plan</a>	
18				
19		21b	Description of any interim analyses and stopping	42
20			guidelines, including who will have access to these	
21			interim results and make the final decision to	
22			terminate the trial	
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and	35-38
26			managing solicited and spontaneously reported	
27			adverse events and other unintended effects of trial	
28			interventions or trial conduct	
29				
30			<a href="#">This point is provided by the vigilance unit of the sponsor.</a>	
31			<a href="#">All details are described in the protocol</a>	
32				
33				
34	Auditing	23	Frequency and procedures for auditing trial conduct, if	44
35			any, and whether the process will be independent	
36			from investigators and the sponsor	
37				
38			<a href="#">Actually and according the risk analysis, no audit is planned</a>	
39				
40	<b>Ethics and dissemination</b>			
41				
42	Research ethics	24	Plans for seeking research ethics	45
43	approval		committee/institutional review board (REC/IRB)	
44			approval	
45			<a href="#">N° IdRCB : 2017-A00008-45</a>	
46				
47				
48			<a href="#">Initial Approval by CPP Nord-Ouest I (Committee for the</a>	
49			<a href="#">Protection of Personnes/Ethic committee) : 25/07/2017</a>	
50			<a href="#">Approval Number: CPP3517-I</a>	
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1				
2	Protocol	25	Plans for communicating important protocol	46
3	amendments		modifications (eg, changes to eligibility criteria,	
4			outcomes, analyses) to relevant parties (eg,	
5			investigators, REC/IRBs, trial participants, trial	
6			registries, journals, regulators)	
7				
8			<a href="#">Each major protocol amendment is submitted to authorities</a>	
9			<a href="#">for approval.</a>	
10			<a href="#">After approval, it is communicated to all the actors of this</a>	
11			<a href="#">project (investigators, trial centers, trial registry ....)</a>	
12				
13	Consent or assent	26a	Who will obtain informed consent or assent from	47
14			potential trial participants or authorised surrogates,	
15			and how (see Item 32)	
16			<a href="#">Principal Investigator or sub-investigator</a>	
17				
18		26b	Additional consent provisions for collection and use of	33; 38; 48
19			participant data and biological specimens in ancillary	
20			studies, if applicable	
21			<a href="#">Not applicable</a>	
22				
23				
24	Confidentiality	27	How personal information about potential and enrolled	43; 47-49
25			participants will be collected, shared, and maintained	
26			in order to protect confidentiality before, during, and	
27			after the trial	
28			<a href="#">Collected by investigators and CRA on each trial centers.</a>	
29			<a href="#">These data are anonymized.</a>	
30			<a href="#">Shared on the eCRF.</a>	
31			<a href="#">There is a control access on the eCRF</a>	
32				
33				
34				
35	Declaration of	28	Financial and other competing interests for principal	Not
36	interests		investigators for the overall trial and each study site	applicable
37			<a href="#">None</a>	
38				
39	Access to data	29	Statement of who will have access to the final trial	48-49
40			dataset, and disclosure of contractual agreements	
41			that limit such access for investigators	
42			<a href="#">Directly on the eCRF</a>	
43				
44				
45	Ancillary and post-	30	Provisions, if any, for ancillary and post-trial care, and	Not
46	trial care		for compensation to those who suffer harm from trial	applicable
47			participation	
48			<a href="#">Not applicable</a>	
49				
50				
51	Dissemination	31a	Plans for investigators and sponsor to communicate	50
52	policy		trial results to participants, healthcare professionals,	
53			the public, and other relevant groups (eg, via	
54			publication, reporting in results databases, or other	
55			data sharing arrangements), including any publication	
56			restrictions	
57				
58				
59			<a href="#">A publication is planned; no publication restriction.</a>	
60				

1 2 3 4 5 6 7 8 9	31b	Authorship eligibility guidelines and any intended use of professional writers	50
		Coordinator will be the first author; co investigators will be authors.	
10 11 12 13 14 15	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
		N/A	

## Appendices

16 17 18 19 20 21 22 23 24 25 26 27 28 29	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional form (not in the protocol)
23 24 25 26 27 28 29	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 <a href="#">Not applicable</a>	59

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\*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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<b>Primary Subject Heading</b>:	Oncology
Secondary Subject Heading:	Urology
Keywords:	prostate cancer, stereotactic body radiation therapy, recurrent prostate cancer, salvage radiotherapy

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Manuscripts

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3 1 **GETUG-AFU 31: a phase I/II multi-center study evaluating the safety and efficacy of salvage**  
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5 2 **stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation**  
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7 3 **therapy; study protocol**  
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8 29  
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10 30 Word count : 5193  
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12 31

13  
14 32 **ABSTRACT**

15  
16 33 Introduction. Prostate cancer is the third most important cancer in terms of mortality in men. No  
17  
18 34 standard local treatment exists for patients with an intraprostatic recurrence after radiotherapy.  
19  
20 35 Stereotatic body radiotherapy (SBRT) could be a curative treatment for local recurrence. The phase I/II  
21  
22 36 primary objective is the selection of the recommended dose for salvage-SBRT and to estimate the  
23  
24 37 efficacy.  
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27  
28 38 Methods and Analysis. We plan to perform a multicenter prospective phase I/II study including at least  
29  
30 39 47 patients. Eligible patients are patients with biochemical recurrence occurring at least 2 years after  
31  
32 40 external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL)  
33  
34 41 and histologically proven intraprostatic recurrence only (stage T1-T2 on relapse, PSA level  $\leq 10$  ng/mL,  
35  
36 42 PSA doubling time  $> 10$  months, absence of pelvic or metastatic recurrence proven by choline or PSMA  
37  
38 43 PET-scan, and pelvic and prostatic assessment by multiparametric MRI).

39  
40 44 The phase I primary objective is the selection of the recommended dose for salvage-SBRT (5 x 6 Gy, 6  
41  
42 45 x 6 Gy, or 5 x 5 Gy) based on dose-limiting toxicity. The dose of salvage-SBRT will be selected using a  
43  
44 46 Time-to-Event Continual-Reassessment-Method based on dose-limiting toxicity defined as grade  $\geq 3$   
45  
46 47 gastrointestinal or urinary toxicity or any other grade 4 adverse event. The phase II primary outcome  
47  
48 48 is to estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate  
49  
50 49 (Phoenix definition: increase in serum total PSA  $\geq 2$  ng/mL above the nadir). Phase II secondary  
51  
52 50 outcomes are acute and late toxicities, quality of life, clinical progression-free survival defined as the  
53  
54 51 time interval between the date of registration and the date of clinical progression or death irrespective  
55  
56 52 of the cause.  
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2  
3 53 Ethics and Dissemination. The study has received ethical approval from the Ethics committee "Ile-de-  
4  
5 54 France III". Academic dissemination will occur through publication and conference presentations.  
6

7 55 **Trial registration:** NCT03438552  
8

9  
10 56 **Date of trial registration:** November 14, 2017  
11

12 57  
13

14 58 **Strengths and limitations of this study funding**  
15

- 16 59 - Very innovative trial evaluating stereotactic body radiotherapy for recurrent prostate cancer,  
17  
18 the only ongoing trial of this kind in Europe to our knowledge  
19 60  
20  
21 61 - Clinical trial supported by the GETUG-AFU cooperative group, expert in the field  
22  
23 62 - Time-to-Event Continual Reassessment Method, a more appropriate method than the 3+3  
24  
25 63 design to quantify late toxicity in phase I radiotherapy trials  
26  
27 64 - Proof-of-concept study; further research will be required  
28  
29  
30 65 - Small sample size  
31

32 66  
33

34 67 **Keywords:** prostate cancer, stereotactic body radiation therapy, recurrent prostate cancer  
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## 81 Background

82 Prostate cancer is the third most important cancer in terms of mortality in men (after lung and  
83 colorectal cancer), and the fourth leading cancer overall [1]. In the European Union, it was predicted  
84 that 72600 patients would die from prostate cancer in 2015. The rate of recurrence/relapse of prostate  
85 cancer after primary external beam radiotherapy varies from 21% to 65% depending on the study [2,3].  
86 Zelefsky et al. performed biopsies on 339 patients after treatment with 3-dimensional conformal  
87 radiotherapy (3D-CRT) or intensity modulated RT for T1c-T3 stage prostate cancer, with a minimum  
88 follow-up of 2.5 years [2]. They found that the rate of positive biopsy according to radiation dose was  
89 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  
90 performed in 312/843 patients included in MRC RT01 trial. A positive biopsy was prognostic of worse  
91 biological progression free survival compared with negative and suspicious biopsies, hazard ratio  
92 (HR)=4.81 (95% confidence interval [CI]: 2.50-9.26, p<0.001). The estimate for survival was HR=1.58  
93 (95% CI: 0.52-4.78, p=0.42).

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

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

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3 107 specific mortality rate of 36% vs. 6% ( $p=0.0001$ ). Thus late relapse and long PSA doubling time are  
4  
5 108 prognostic factors of solely intraprostatic relapse.

6  
7 109 Prostate-specific antigen (PSA) is a validated biomarker for prostate cancer. PSA levels are  
8  
9 110 extensively used to monitor response to radical prostatectomy (RP) and external-beam radiotherapy  
10  
11 111 (EBRT). The serum PSA level is an important surrogate for recurrence in prostate cancer patients. The  
12  
13 112 recommendations of the Radiation Therapy Oncology Group (RTOG) ASTRO Phoenix Consensus  
14  
15 113 Conference suggested that an increase of  $\geq 2$  ng/mL from the nadir be used to define  
16  
17 114 recurrence/relapse [6]. It is important to note that biochemical recurrence may indicate local or  
18  
19 115 systemic disease recurrence, and may require prostate biopsy for confirmation particularly when local  
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21 116 salvage treatments are being considered [7].

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24  
25 117 A number of different salvage treatments have been used after failure of primary radiotherapy. RP  
26  
27 118 is more invasive than brachytherapy, ultrasound, high-intensity focused ultrasound (HIFU), and SBRT.  
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29 119 Below is a brief discussion of the results obtained with each techniques and its associated toxicity and  
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31 120 complications.

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34 121 Salvage RP (SRP) is a treatment option after local recurrence following EBRT. However, the  
35  
36 122 morbidity, including incontinence and erectile dysfunction, is higher than that observed with first-line  
37  
38 123 RP patients. A systematic literature review [7] reported that the probability of biochemical relapse–  
39  
40 124 free survival (bRFS) following SRP in prostate cancer patients was 47-82% after 5 years and 28-53%  
41  
42 125 after 10 years. SRP has an increased risk of adverse events due to fibrosis and poor wound healing  
43  
44 126 after radiotherapy. Furthermore, SRP after radiotherapy compared to primary RP has a significantly  
45  
46 127 higher rate of urinary and gastrointestinal morbidity [8]. The review above [7], reported that the most  
47  
48 128 frequent complications were anastomotic stricture (7-41%) and rectal injury (0-28%). The majority (50-  
49  
50 129 91%) of men had erectile dysfunction before SRP and 80-100% after surgery. Post-operative urinary  
51  
52 130 continence ranged from 21-90%.

53  
54  
55  
56 131 In a recent review, salvage brachytherapy after EBRT is reported to achieve biochemical control  
57  
58 132 rates of 20% to 89% (median follow-up: 19 to 108 months) [9]. Rates of genitourinary toxicities range



1  
2  
3 133 from 12% to 87% for grade 1-2, and 3% to 47% for grade 3-4 toxicities. Similarly, the rates of  
4  
5 134 gastrointestinal toxicities range from 4% to 65% for grade 1-2, and 0% to 20% for grade 3-4 toxicities.  
6  
7 135 Erectile dysfunction was observed in 2% to 95% of men. A phase II study of salvage high-dose-rate  
8  
9 136 brachytherapy (HDR) for treating recurrent prostate cancer after definitive external beam  
10  
11 137 radiotherapy was reported by Yamada [10]. The 42 patients enrolled, with biopsy proven recurrence,  
12  
13 138 were treated with salvage HDR (iridium-192) with a resulting bRFS at 5 years of 68.5% (median follow-  
14  
15 139 up of 36 months [range: 2-66 months]). Acute genitourinary toxicity was observed: grade 1, 38% of  
16  
17 140 patients and grade 2: 40%. Similarly, late genitourinary toxicity was observed: grade 1, 38% of patients  
18  
19 141 and grade 2, 48%. In addition, 1 patient had a grade 3 urinary incontinence and 3 had grade 3 urethral  
20  
21 142 strictures. Late gastrointestinal toxicities were observed: grade 1, 43% of patients and grade 2, 14%.  
22  
23 143 More recently, a study of 83 prostate cancer patients with local recurrence after radiotherapy treated  
24  
25 144 with high-dose-rate brachytherapy was reported [11]. The 3-year and 5-year bRFS were 76% and 67%.  
26  
27 145 A phase II study of the RTOG in 100 patients was recently presented: twelve (14%) experienced late  
28  
29 146 grade 3 genitourinary/gastrointestinal adverse effects. This rate of late grade 3 toxicity (14%) was not  
30  
31 147 unacceptable by the predetermined protocol specification, without any grade 4-5 events. The only  
32  
33 148 factor predictive of late toxicity was implant dose, underlining the need for meticulous planning and  
34  
35 149 technique to limit the final delivered dose [12]. In France, a phase II study, "Brachytherapy for  
36  
37 150 Recurrent Prostate Cancer" (CAPRICUR) was recently completed [13].  
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43 151 HIFU is another less invasive salvage treatments following recurrence. HIFU uses focused  
44  
45 152 ultrasound to generate heat (85°C) which induces tissue necrosis [14]. The following studies have  
46  
47 153 investigated the use of salvage-HIFU after initial radiotherapy. A French group treated 290 men with  
48  
49 154 biopsy-confirmed recurrent prostate cancer, after radiotherapy, with salvage HIFU [15]. At 7 years, the  
50  
51 155 cancer-specific survival rate was 80% and the metastasis-free survival rate was 79.6%. Recto-urethral  
52  
53 156 fistula occurred in 0.4% of patients and 19.5% had grade 2/3 incontinence. Half of the patients also  
54  
55 157 received hormone therapy. Survival without relapse at 5 years after HIFU, by D'Amico risk groups prior  
56  
57 158 to their initial treatment, was 45% (favorable), 31% (intermediate risk) and 21% (high risk). In this  
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3 159 cohort, the grade  $\leq 3$  urinary incontinence levels were 23% (favorable), 14% (intermediate risk) and 9%  
4  
5 160 (high risk). Nearly 8% of patients required an artificial sphincter following HIFU. Importantly, pubic  
6  
7 161 osteitis occurred in 2.5% of patients despite adherence to parameters specific to HIFU following  
8  
9  
10 162 radiotherapy [15].

11  
12 163 Cryotherapy is thermo-ablative treatment; the third-generation argon/helium-based cryotherapy  
13  
14 164 system creates precise isotherms through ultrathin needles [16]. In a retrospective multicenter series  
15  
16 165 pooling 279 patients, survival without biochemical relapse at 5 years was 54%. Prostatic biopsies  
17  
18 166 showed tumor persistence in 32% of patients following cryotherapy [17]. In a paired case-controlled  
19  
20 167 study, prostatectomy and cryotherapy were compared following radiotherapy. Survival without  
21  
22 168 relapse (PSA nadir + 0.4 ng/mL) at 5 years was significantly lower after cryotherapy (21% vs. 61%,  
23  
24 p<0.001); this was confirmed by the 5-year OS rate of 85%, cryotherapy, vs 95%, radical prostatectomy  
25  
26 169 (p=0.001) [18]. Intermediate results from a study investigating third-generation cryotherapy as a  
27  
28 170 salvage treatment of locally recurrent prostate cancer after radiotherapy was published [19]. The 5-  
29  
30 171 year bRFS rate (Phoenix definition) was 43.5% and with a 5-year OS rate of 92.3%. Mild complications  
31  
32 172 (grades 1 and 2) were reported including: mild incontinence (9.4%), acute rectal pain (31.3%), lower  
33  
34 173 urinary tract symptoms (15.6%) and erectile dysfunction (57.1%). Grade 3 toxicities: incontinence  
35  
36 174 (3.1%) and urethral sloughing (3.1%) were observed.  
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41 176 Androgen-deprivation therapy (ADT) alone (continuous or intermittent) is commonly given to  
42  
43 177 patients with biochemical relapse after radiotherapy [20]. In a series based on data from a North  
44  
45 178 American national registry (CaPSURE), 71% of patients were treated for biochemical relapse after  
46  
47 179 prostatectomy or radiotherapy. ADT was initiated in 93% of these patients, and the remaining patients  
48  
49 180 were treated with surgery, brachytherapy, cryotherapy, or repeat external radiotherapy [21]. ADT may  
50  
51 181 cause adverse effects impacting patient's quality of life (including: hot flushes, erectile dysfunction and  
52  
53 182 reduced libido, cognitive impairment, and anemia). The metabolic changes associated with hormone  
54  
55 183 therapy may also increase the risk of cardiovascular morbidity. The reduction in bone mass is maximal  
56  
57 184 in the first year and increases with the duration of castration; the risk of fracture is increased in patients  
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3 185 surviving for more than 5 years [22-23]. The guidelines suggest that a simple follow-up can be  
4  
5 186 implemented for local recurrence in patients with a limited life expectancy or for those who do not  
6  
7 187 wish to undergo local salvage treatment. The last European Association of Urology guidelines [24]  
8  
9 188 recommended to perform salvage surgery in experienced centres due to the increased rate of side  
10  
11 189 effects. It is recommended to offer/discuss HIFU, cryosurgical ablation and salvage brachytherapy  
12  
13 190 to/with patients without evidence of metastasis and with histologically proven local recurrence and to  
14  
15 191 inform patients about the experimental nature of these approaches. The level of evidence for each of  
16  
17 192 these recommendations is 3 [24].  
18  
19

20  
21 193 SBRT delivers highly conformal, high-dose radiation in a few fractions (hypofractionation), typically  
22  
23 194 5 to 7 fractions for prostate cancer. It is reported that tissues with a low  $\alpha/\beta$  ratio, as for prostate  
24  
25 195 cancer, are more sensitive to large doses of radiation per fraction. The surrounding normal tissue could  
26  
27 196 have similar or higher  $\alpha/\beta$  ratio. This suggests that hypofractionation (large radiation dose per fraction)  
28  
29 197 may result in improved tumor control with limited toxicity. A pooled analysis of 1100 patients included  
30  
31 198 in separate prospective phase II studies in 8 institutions was performed to evaluate the effectiveness  
32  
33 199 of SBRT as a first-line treatment for localized prostate cancer [25]. The SBRT was delivered by  
34  
35 200 CyberKnife with a median dose of 36.25 Gy in 4-5 fractions. The 5-year bRFS rate was 93% for all  
36  
37 201 patients. Thus relapse-free survival rates after SBRT compare favourably with other definitive  
38  
39 202 treatments for low and intermediate-risk patients with a short follow up. SBRT is well tolerated with a  
40  
41 203 low effect on quality of life [25-28]. In addition sexual function appeared to be spared in the majority  
42  
43 204 of patients [25-28].  
44  
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48 205 SBRT has also been used as a salvage treatment following failure of external radiotherapy.  
49  
50 206 Jereczek-Fossa et al. published data on 34 consecutive patients treated with robotic SBRT for isolated  
51  
52 207 recurrent primary, lymph node, or metastatic prostate cancer [29]. Of the 34 patients, 15 patients had  
53  
54 208 intraprostatic recurrence, confirmed by biopsy, and were treated with SBRT (CyberKnife) with a  
55  
56 209 median dose of 30 Gy in 5 fractions. Fourteen patients showed a biochemical response; the median  
57  
58 210 survival without recurrence was 13 months. Five patients presented a clinical relapse, including one  
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3 211 new intraprostatic recurrence. Urinary toxicity was low, with a grade 3 urinary toxicity in only one  
4  
5 212 patient. No case of acute or late gastrointestinal toxicity was reported. This good gastrointestinal  
6  
7 213 tolerability has subsequently been confirmed [29-32]. In Fuller et al twenty-nine patients were treated  
8  
9 214 in a phase II trial with stereotactic radiotherapy for intraprostatic recurrence [30]. Eligible patients had  
10  
11 215 to present biopsy-proven intraprostatic recurrence graded T1 to T3N0M0 more than 2 years post-  
12  
13 216 radiotherapy and without a pre-existing grade >1 radiotherapy toxicity. The prior median dose  
14  
15 217 delivered was 73.8 Gy and the median interval between the treatments was 88 months. The dose  
16  
17 218 delivered to the entire gland was 34 Gy in five fractions over 5 days (heterogeneous intraprostatic dose  
18  
19 219 of up to 50 Gy). With a median follow-up of 24 months, survival without recurrence was 82%. Toxicity  
20  
21 220 was acceptable, with 18% grade  $\geq 2$  urinary toxicity, including one patient with a grade 4 toxicity, and  
22  
23 221 no late gastrointestinal toxicity above grade 1. Particular attention should be given to patients who  
24  
25 222 still exhibit urinary toxicity after initial radiotherapy [30]. Our preliminary retrospective results in 23  
26  
27 223 patients treated for this indication were published recently [31]. A total dose of 36 Gy was prescribed  
28  
29 224 in 6 fractions of 6 Gy. Nineteen patients had a whole-gland and four a partial treatment. Median follow-  
30  
31 225 up was 23 months (range 6 to 40 months). We observed no grade 4 or 5 toxicity. Two patients  
32  
33 226 presented grade 3 toxicities. Others toxicities include urinary (5 grade 2 and 9 grade 1) and rectal  
34  
35 227 toxicities (2 grade 2 and 2 grade 1). The dose levels selected in our study are close to those used in de  
36  
37 228 novo patients, and the same as those described in retrospective salvage treatment series. These  
38  
39 229 schemes seem to provide an acceptable compromise between efficacy and toxicity but have not been  
40  
41 230 evaluated prospectively.

42  
43 231 To date, no standard local treatment exists for patients with an intraprostatic recurrence after  
44  
45 232 radiotherapy [33]. A number of treatments options exist including: radical prostatectomy,  
46  
47 233 brachytherapy, HIFU, cryotherapy, and stereotactic radiotherapy. The literature to date consists  
48  
49 234 mainly of retrospective and small prospective series making it difficult to assess and compare these  
50  
51 235 techniques. In recent years, SBRT has been used to treat localized prostate cancer in the primary  
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53 236 setting but also as a salvage treatment after failure of radiotherapy. The initial results of these  
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3 237 retrospective studies are promising, with respect to survival and tolerance, but further studies are  
4  
5 238 required to confirm these initial results. Our proposed study will provide further evidence of SBRT as  
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7 239 a supplementary non-invasive curative treatment for local recurrence following radiotherapy. This  
8  
9 240 study could provide the foundation for prospective studies comparing the available salvage treatments  
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12 241 after radiotherapy.  
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14 242

### 16 243 **Methods/design**

18  
19 244 This study is approved by the Ethics committee "Ile de France III" (2017-A00008-45) and is registered  
20  
21 245 on [clinicaltrials.gov](http://clinicaltrials.gov) (NCT03438552). This multicenter open-labelled phase I/II study will initially select  
22  
23 246 the SBRT scheme (phase I), either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy. The effectiveness of SBRT scheme  
24  
25 247 selected in phase I will then be evaluated in a single-arm multicenter phase II study.

27 248 PHASE I primary objective and assessment:

29  
30 249 Selection of the recommended dose for salvage-SBRT (either 5 x 6 Gy, 6 x 6 Gy, or 5 x 5 Gy) based on  
31  
32 250 dose-limiting toxicity observed during the 18 weeks following the initiation of salvage-SBRT. The dose  
33  
34 251 of salvage-SBRT will be selected using a Time-to-Event Continual Reassessment Method [34-36] based  
35  
36 252 on dose-limiting toxicity defined as grade  $\geq 3$  gastrointestinal or urinary toxicity or any other grade 4  
37  
38 253 adverse event observed during the 18 weeks following the initiation of salvage-SBRT.

40 254 PHASE II primary objective and assessment:

42  
43 255 Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate (Phoenix  
44  
45 256 definition: increase in serum total PSA  $\geq 2$  ng/mL above the nadir). Time to biochemical relapse-free  
46  
47 257 survival will be computed from registration. Patients alive without biochemical progression at the time  
48  
49 258 of the analysis will be censored at the last follow-up date. In the event of death, whatever the cause  
50  
51 259 of death, the patient will be considered as a failure.

53 260 PHASE II secondary objective(s) and assessment:

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3 263      ○ Acute and late genitourinary and gastrointestinal toxicities over the first 3 years according to  
4  
5 264      the NCI-CTCAE V4.03 classification (June 14th, 2010), International prostate Symptom Score  
6  
7 265      (IPSS) score for urinary symptoms, and International Index of Erectile Function (IIEF5) for  
8  
9  
10 266      erectile function. Patients will be followed for 5 years after salvage SBRT to assess late toxicity.  
11  
12 267      Patients with second biochemical recurrence will not be excluded in order to assess late  
13  
14 268      toxicity.
- 15  
16 269      ○ Quality of life will be evaluated based on the EORTC QLQ-C30 and QLQ-PR25 scales. The Time  
17  
18 270      Until Definitive Deterioration (TUDD) will be computed from registration until the first  
19  
20 271      observation of a definitive deterioration of the quality of life, defined as a score decreased by  
21  
22 272      10 points (in the case of global health scale and functional scales) or increased by 10 points (in  
23  
24 273      the case of symptom scales) compared to the score at baseline, without later improvement  
25  
26 274      superior to 10 points compared to baseline score.
- 27  
28 275      ○ Clinical progression-free survival is defined as the time interval between the date of  
29  
30 276      registration and the date of clinical progression (local progression assessed by the physical  
31  
32 277      examination, or appearance of metastatic lesions) or death irrespective of the cause.
- 33  
34 278      ○ Overall survival is defined as the time interval between the date of registration and the date  
35  
36 279      of death irrespective of the cause.
- 37  
38 280      ○ Erythroblast transformation-specific related gene (ERG) fusion expression will be evaluated  
39  
40 281      using immunohistochemistry (IHC) tests. ERG fusion and androgen-receptor splice variant 7  
41  
42 282      (ARV7) expression will be evaluated on biopsies before the first radiotherapy treatment (at  
43  
44 283      diagnosis, if available) and before salvage radiotherapy after biochemical recurrence.  
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52 285      **DIAGNOSIS AND INCLUSION CRITERIA:**

- 53  
54 286      ○ Biochemical recurrence occurring at least 2 years after external radiotherapy  
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56 287      for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL)  
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- T1–T2c and PSA  $\leq 20$  ng/mL and Gleason score  $\leq 7$  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  $\leq 10$  ng/mL at baseline (before salvage-SBRT)
  - PSA doubling time  $> 10$  months
  - IPSS  $\leq 12$
  - 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

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3 314                   ○ Life-expectancy greater than or equal to 5 years (Lee scale)  
4  
5 315                   ○ Patient registered with a health insurance system  
6  
7 316                   ○ Patient who has signed the informed consent form  
8  
9  
10 317                   ○ Patients willing and able to comply with the scheduled visits, treatment plan,  
11  
12 318                   laboratory tests, and other study procedures indicated in the protocol.  
13

14 319 EXCLUSION CRITERIA:

- 15  
16 320                   ○ Lymph node or metastatic spread  
17  
18 321                   ○ Late post-radiotherapy urinary or gastrointestinal toxicity of grade  $\geq 2$   
19  
20 322                   (following primary radiotherapy)  
21  
22  
23 323                   ○ Other cancers in the last 5 years except for non-melanoma-type skin cancer  
24  
25 324                   ○ History of inflammatory bowel disease  
26  
27  
28 325                   ○ Anticoagulant treatment  
29  
30 326                   ○ Contraindications to undergoing MRI  
31  
32 327                   ○ Prostate volume > 80 cc  
33  
34 328                   ○ Transurethral resection of the prostate (TURP) in the 6 months before  
35  
36 329                   registration  
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39 330                   ○ Presence of rectal telangiectasia grade 3 classified by the Vienne Rectoscopy  
40  
41 331                   Score (obligatory rectoscopy) [37,38]  
42  
43 332                   ○ Previous rectal surgery  
44  
45 333                   ○ Patients unable to undergo medical follow-up in the study for geographical,  
46  
47 334                   social or psychological  
48  
49  
50 335                   ○ Person deprived of their liberty or under protective  
51

52 336 INTERVENTION

53  
54 337                   A flow chart presenting the different steps from inclusion until treatment is presented in Fig. 1. Five  
55  
56 338                   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  
57  
58 339                   over a maximum of 12 days to provide a total dose of 25 to 36 Gy. This radiotherapy may be  
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3 340 administered with the CyberKnife® or a linear accelerator allowing stereotactic radiotherapy. The  
4  
5 341 patient will be placed in a stable and reproducible supine position. Intraprostatic markers (fiducials)  
6  
7 342 will be implanted before the dosimetric CT-scan and MRI are performed. The choice of markers is left  
8  
9  
10 343 to the discretion of each participating site (gold seeds, etc.). The site needs to ensure that the  
11  
12 344 repositioning of the prostate is precise ( $\leq 2$  mm), allowing an exact overlay between dosimetric MRI  
13  
14 345 and computed tomography (CT)-scan. The implant of fiducials is obligatory irrespective of the  
15  
16 346 stereotactic radiotherapy technique used. The fiducials can be implanted during or after the biopsies.  
17  
18 347 The CT-scans and MRIs registration is guided by the fiducials. Each team can choose the fiducials visible  
19  
20 348 on the MRI they wish to use and/or integrate a specific sequence during the centering MRI for better  
21  
22 349 visualization.

23  
24  
25 350 An mpMRI and CT-scan will be carried out at least one week after fiducial implantation. CT-scan  
26  
27 351 images should be acquired with the patient in the treatment position using the chosen immobilizing  
28  
29 352 system, if required according to centers' standard procedures. An intravenous injection of a contrast  
30  
31 353 product should be administered unless contraindicated. Acquisition should allow anatomical  
32  
33 354 structures and markers (already implanted in the prostate) to be visualized. The bladder will be half-  
34  
35 355 filled (neither full nor empty, i.e. a final voiding 90 minutes before the CT-scan followed by ingestion  
36  
37 356 of 250-350 mL of water). The rectum will be empty and not distended. If necessary rectal enema can  
38  
39 357 be used before CT-scan acquisition. Contiguous CT-scan slices  $\leq 2$  mm thick will be taken between the  
40  
41 358 L5-S1 joint space and the small trochanters. After image transfer to a planimetric console, fiducial-  
42  
43 359 based registration with the prostatic mpMRI will take place in order to provide a better definition of  
44  
45 360 the Gross Target Volume (GTV) and prostatic contours, especially the apex. Fiducial-based CT-MRI  
46  
47 361 registration is mandatory. Multimodality image registration with Choline PET is possible but not  
48  
49 362 mandatory.

50  
51 363 Delineation of the target volume will be carried out by a radiotherapist experienced in the definition  
52  
53 364 of prostate volumes on CT-scans and MRIs. The mpMRI-defined contour will be integrated with the CT-  
54  
55 365 scan derived contours in order to define tumor and the prostatic apex more precisely. GTV will be  
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3 366 represented by lesion defined on the multiparametric MRI +/- choline PET; a 5-7 mm margin around  
4  
5 367 the GTV will be used to define the Clinical Target Volume (CTV). CTV is contained in the prostate, except  
6  
7 368 in the case of extracapsular extension (unilateral extracapsular extension on MRI permitted except  
8  
9  
10 369 posteriorly relative to the rectum). In the case where the positive biopsy(ies) are outside and adjacent  
11  
12 370 to the visible lesions on the MRI, the zone containing these biopsies must be included in the CTV so  
13  
14 371 that the prostate cancer recurrence not visible on the MRI is included in the CTV. If no lesion is visible  
15  
16 372 on the MRI and/or choline PET, the zone containing positive biopsies must be included in the CTV. For  
17  
18 373 example: MRI +/-choline PET lesion in 3p and 4p according to ESUR guidelines, with positive biopsies  
19  
20 374 in 1p, 3p and 4p: CTV = MRI GTV + 5 mm + the posterior right base. The total CTV should not be more  
21  
22 375 than half of the total volume of the prostate by MRI. The planning target volume (PTV) will be obtained  
23  
24 376 by an expansion of 2 mm around the CTV in this repeat radiotherapy context. This margin involves that  
25  
26 377 the probability of coverage at 25, 30, or 36 Gy is low, so the reporting will include D2%, 50%, D98%  
27  
28 378 and D95% to describe as much as possible delivered dose. Organs at risk constraints are specified in  
29  
30 379 Table 1. Daily image guided radiation therapy is mandatory, intra fraction tracking is recommended.  
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380	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 <sub>max</sub> (35 mm <sup>3</sup> ) <39 Gy
			V36 Gy <1 cc

381  
382 Table 1. Organs at risk constraints  
383

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

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2  
3 389 dosimetric data will be subject to a centralized review prior to SBRT administration in order to verify  
4  
5 390 that constraints are being observed. Follow-up visits are described in Figures 1 and 2.  
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8 391

#### 9 392 SAMPLE SIZE CALCULATION

10 393 Required number of patients to be included: minimum 47 patients. The total sample size will depend  
11  
12 394 upon the number of patients allocated at the different dose levels in the dose-finding parts of the trial.  
13  
14 395 A minimum of 13 patients will be recruited before the expansion phase is open (Phase II part). A total  
15  
16 396 of 44 patients allocated at the recommended dose (recruited in the dose-escalation stage or in the  
17  
18 397 expansion phase) and evaluable at 3 years are required for the main analysis of the Phase II part of the  
19  
20 398 trial to ensure an 85%-power if 3-year bRFS is  $p_1=0.70$ , with a test against  $p_0=0.50$  at a one-sided 5%-  
21  
22 399 alpha level.  
23  
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#### 29 401 STATISTICAL CONSIDERATIONS

##### 30 402 PHASE I

31  
32 403 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  
33  
34 404 is 5 x 6 Gy. The lower dose level, 5 x 5 Gy, will be considered if excessive toxicity is reported at the first  
35  
36 405 dose-level (5 x 6 Gy). A TimeTo Event-Continuous Reassessment Method (TITE-CRM) with an empiric  
37  
38 406 dose-toxicity model in a Bayesian framework will be used for the dose-finding part of the trial to  
39  
40 407 identify the recommended dose. The target dose limiting toxicity (DLT) probability is set at  
41  
42 408  $p(\text{DLT})=0.25$ . Observations of patients who have no DLT at the time of the analysis but have not  
43  
44 409 completed the DLT assessment period will be down-weighted in the likelihood, proportionally to the  
45  
46 410 length of follow up; for instance, if the last patient has been recruited 8 weeks before a new patient is  
47  
48 411 available for enrolment, and is evaluated at week 10 with no DLT, then his observation is attributed a  
49  
50 412 weight of  $10/18=0.56$ .  
51  
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56 413 At least three patients will be enrolled at the first dose-level and fully evaluated over the 18-week  
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58 414 study period before the dose is escalated to the next dose-level. Radiation dose levels for further  
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3 415 patients will be defined based on the estimate of the probability of DLT at each dose-level considering  
4  
5 416 all available information accumulated so far. Patients will be treated at the best current estimate of  
6  
7 417 the recommended dose i.e. the dose associated with an estimated probability of DLT the closest to the  
8  
9 418 target 0.25. Patients may eventually be treated at a dose below the dose recommended by the model  
10  
11 419 for safety reasons. The patients can be recruited with no minimal time interval between successive  
12  
13 420 inclusions. During the dose-escalation part of the trial, safety data will have to be reported in the data  
14  
15 421 base in real time. A monthly teleconference meeting with the participation of the biostatistician, the  
16  
17 422 trial coordinator and a representative of the sponsor, to summarize toxicity observations and define  
18  
19 423 the dose to be allocated to the next patient(s) will be held. Safety data will be discussed with an  
20  
21 424 Independent Data Monitoring Committee (IDMC) at the end of the dose-escalation part of trial, or  
22  
23 425 before if needed.

24  
25  
26  
27 426 The dose-escalation part of the study will terminate once 10 patients have been treated and evaluated  
28  
29 427 at a dose currently identified as the recommended dose. Further patients will then be accrued in the  
30  
31 428 expansion cohort, where toxicity data collected over the first 18-week period and DLT assessment will  
32  
33 429 be analyzed approximately every 10 patients with the possibility of modification of the recommended  
34  
35 430 dose, based on model-based estimates.

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39 431 Specifications of the model are detailed in appendix, as well as the results of a simulation study  
40  
41 432 evaluating the operating characteristics of the proposed design.

#### 42 43 433 PHASE II

44  
45 434 The phase II is based on a one-stage design based on an efficacy endpoint (3-year bRFS). Assuming that  
46  
47 435 information will be available for all patients at 3 years, the endpoint follows a binomial distribution.

48  
49 436 The design was thus defined considering exact tests, as published by A'Hern [39].

50  
51  
52 437 From the literature, the expected bRFS rate at 3 years is approximately 50% in this patient population  
53  
54 438 with various salvage therapies. A 3-year bRFS equal to or lower than 0.50 is deemed insufficient for  
55  
56 439 further evaluation of this approach [ $p_0=0.50$ ]. The considered alternative hypothesis is  $p_1=0.70$ ].  
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3 440 The Phase II part of the study will need to include 44 patients (including the patients recruited in the  
4  
5 441 dose-finding part of the phase I, allocated at the dose level finally identified as the recommended  
6  
7 442 dose). If all 44 patients are evaluable at 3 years, the treatment strategy will be considered to be  
8  
9 443 insufficiently effective if  $\leq 27$  patients are alive without a biochemical relapse at 3 years.

10  
11  
12 444 The operating characteristics of the design are:

- 13  
14 445 ○  $p_0=0.50, p_1=0.70$
- 15  
16 446 ○ Defined Type I error = 0.05 (computed type-I error of the design = 0.048)
- 17  
18 447 ○ Defined Power = 0.85 (computed power = 0.861)

19  
20  
21 448 If some patient data are censored before 3 years, the 3-year bRFS will be estimated using Kaplan-Meier  
22  
23 449 method and the lower boundary of the 90% confidence interval will be compared to  $p_0=0.50$ . The  
24  
25 450 conclusion will be positive if we can reject the null hypothesis  $p_0=0.50$  at a one-sided 5% alpha level.

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28 451

## 29 30 452 PATIENT AND PUBLIC INVOLVEMENT

31  
32 453 Patients were not involved in the idea conception of this trial.

33  
34 454 Patients were not involved in the design of this study nor in recruitment of the study.

35  
36  
37 455

## 38 39 456 Ethics and Dissemination

40  
41 457 The study has been submitted and approved by ethics committee "Ile de France III" (2017-A00008-45)  
42  
43 458 for all study sites. A written informed consent will be obtained from the study participants. In France,  
44  
45 459 according to the current law, a protocol can be subjected to any regional Ethics Committee, even if no  
46  
47 460 hospital of this region takes part to the trial. The choice is made according to the workload of every  
48  
49 461 committee. The opinion of this Ethics Committee applies to all the national centers. Academic  
50  
51 462 dissemination will occur through publication and conference presentations.

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## 467 Discussion

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

477 The sensitivity of PSMA-PET is higher than that of choline-PET for the detection of lymph node disease  
478 [41]. Unfortunately PSMA PET is not routinely available in France. A modification of the inclusion  
479 criteria is being drafted to allow PSMA PET if this examination becomes available during the study  
480 period. To have a high sensitivity, a surgical lymph node staging must be extensive, which can have  
481 side effects in this context. Furthermore clinical and biological selection criteria (no high risk cancer  
482 before first treatment, PSA level, PSA doubling time,...) are designed to select the patients to have  
483 most likely intra-prostatic recurrence only.

484 The phase I part of GETUG-AFU 31 trial will evaluate SBRT dose of 30 Gy in 5 fractions, over 12 days,  
485 and then depending on tolerance, 36 Gy in 6 fractions over 12 days. The latter, 36 Gy in 6 fractions, is  
486 the current scheme used at the Oscar Lambret Centre for all repeat SBRT. This dose is higher than that  
487 described by Jereczek-Fossa et al. (30 Gy in 5 fractions) [29], discussed as being too low [30], but lower  
488 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  
489 [32]. We have decided to initially use a phase I study, using dose-limiting toxicity criteria, to establish  
490 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  
491 radiotherapy trials, late complications are often not taken into account and there is currently no  
492 consensus on the methodology used for these studies. Although most phase I radiotherapy studies use

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3 493 a 3+3 design, it is not suitable for these studies as it does not assess late toxicity. More complex designs  
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5 494 such as the TITE-CRM are recommended, which will shorten the duration of the entire trial and  
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7 495 efficiently uses patient information throughout the study [42].  
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## 12 498 Abbreviations

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16 499 GETUG-AFU: “Groupe d’Etude des Tumeurs Uro Genitales- Association Française d’Urologie”; PSA:  
17  
18 500 prostate-specific antigen; RP: radical prostatectomy; EBRT: external-beam radiotherapy; SBRT:  
19  
20 501 stereotactic body radiation therapy; HIFU: high-intensity focused ultrasound; bRFS: biochemical  
21  
22 502 relapse-free survival; HDR: high dose rate; RTOG: radiation therapy oncology group; ADT: androgen-  
23  
24 503 deprivation therapy; CTCAE: common toxicity criteria adverse events; Gy: Gray; TITE-CRM: Time-to-  
25  
26 504 Event Continual Reassessment Method; IIEF: International Index of Erectile Function; CTV: clinical  
27  
28 505 target volume; PTV: planning target volume; QOL: Quality of life; RTOG: Radiation Therapy Oncology  
29  
30 506 Group; TUDD: time until definitive deterioration; ERG: Erythroblast transformation-specific related  
31  
32 507 gene; IHC: immunohistochemistry; ARV7: Androgen-receptor splice variant 7; MRI: magnetic  
33  
34 508 resonance imaging; TURP: transurethral resection of the prostate; CT: computed tomography; mpMRI:  
35  
36 509 multiparametric MRI; PET: positron emission tomography; WHO: world health organization; GTV: gross  
37  
38 510 tumor volume; DLT: dose limiting toxicity  
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## 45 513 **Declarations**

46 514

### 47 515 Availability of data and material

48 516 The data set used and/or analysed during the current study are available from the corresponding  
49  
50 517 author on reasonable request. Not all data are obtained yet since the study is still ongoing.  
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3 519 Competing interests  
4

5 520 None declared.  
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8 521  
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13

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15

16 525 body had no role in the design of the study, collection, analysis, and interpretation of data and in  
17

18 526 writing the manuscript.  
19  
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21 527  
22

23 528 Author contributions  
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25 529 Study Conception: DP. Revision of study design and protocol: DP, MCLD, ET, LC, MD, SN, ERL. Study  
26

27 530 coordination: DP, MCLD, ET, SN. All authors read and approved the final manuscript.  
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34 533 None  
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#### 667 **Figures legends**

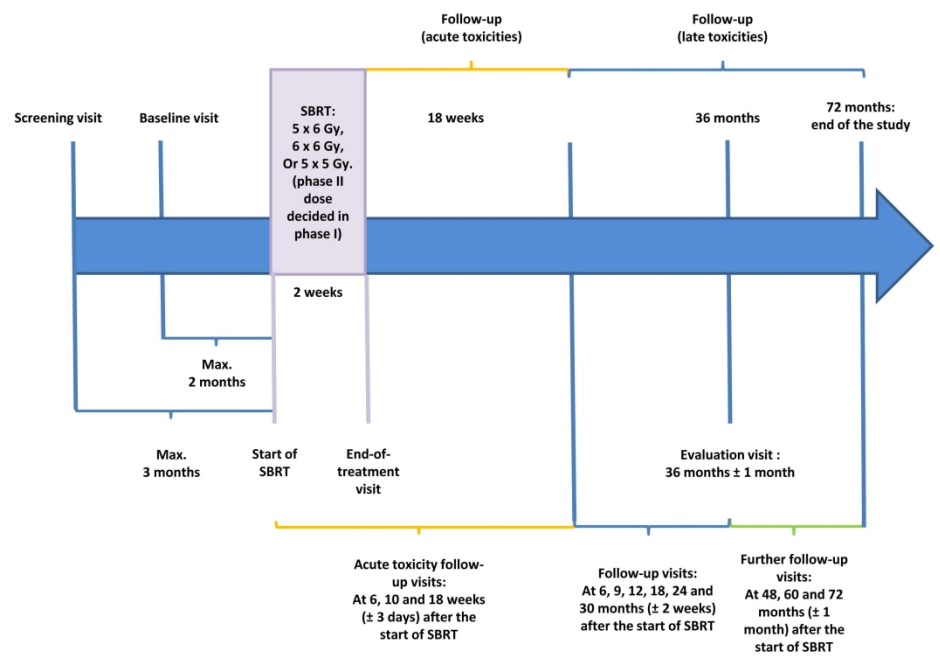
668 Fig. 1 Overview of study flow chart. SBRT: stereotactic body radiotherapy

669 Fig 2. Detailed description of study flow chart.

670 (1.Patient will be contacted by phone 14 weeks after starting SBRT to assess toxicity; an additional visit may be scheduled if required; 2  
671 .Before inclusion, during regular follow-up and in case of biochemical recurrence after SBRT; 3 .Before inclusion and in case of biochemical  
672 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  
673 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		
				End RT	W6	W10	W14 <sup>1</sup>	W18	M6	M9	M12	M18	M24	M30	M36	M48	M60	M72/End of Study
<b>Visits</b>	ScV	BV																
Eligibility criteria	X	X																
Signed informed consent form	X																	
Enrollment in the study		X																
<b>CLINICAL EXAMINATION</b>																		
Weight, height <sup>4</sup> PS (WHO)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Digital rectal examination (clinical stage)	X	X <sup>5</sup>						X	X	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	X
<b>QUESTIONNAIRES</b>																		
QLQ-C30 and QLQ-PR25		X					X	X	X	X	X	X	X	X	X	X	X	X
IPSS		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
IIEF5		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>LABORATORY TESTS</b>																		
CBC, platelets		X																
PT, PTT, and INR		X																
PSA		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>PATHOLOGICAL EVALUATION</b>																		
Gleason score; number of positive biopsies; total number of biopsies; total length of cancer on biopsies; total length of biopsies	X																	
<b>PARACLINICAL INVESTIGATION</b>																		
Multi-parametric MRI (pelvic and prostate)		X <sup>2</sup>					X	X	X	X	X	X	X	X	X	X	X	X
Choline PET scan		X <sup>3</sup>																
TNM evaluation		X																
<b>TRANSLATIONAL RESEARCH</b>																		
Prostate tumor biopsies (Initial before any treatment and at recurrence before SBRT)		X <sup>6</sup>																

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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3 **GETUG-AFU 31: a phase I/II multi-center study evaluating the efficacy of repeat stereotactic**  
4 **radiation in patients with intraprostatic tumor recurrence after external radiation therapy.**  
5

6 **Appendix: statistical model, simulation study**  
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8

9  
10 **Statistical considerations**  
11

12 A TITE-CRM method with an empiric dose-toxicity model in a Bayesian framework will be used for the  
13 dose-finding part of the trial to identify the recommended dose. The target dose-limiting toxicity  
14 (DLT) probability is set at  $p(\text{DLT})=0.25$ . Three dose levels of SBRT are to be considered: 5 x 5 Gy (DL-  
15 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  
16 explored in case of DLT at the starting dose level. DLTs are evaluated during the 18 weeks following  
17 the initiation of salvage-SBRT. Observations of patients who have no DLT at the time of the analysis  
18 but have not completed the DLT assessment period will be down-weighted in the likelihood,  
19 proportionally to the length of follow up.  
20

21  
22 The Phase I part of the study will include 3 patients at the first dose level. Radiation dose levels for  
23 further patients will be defined based on the estimate of the probability of DLT at each dose-level  
24 considering all available information accumulated so far. Patients will be treated at the best current  
25 estimate of the recommended dose i.e. the dose associated with an estimated probability of DLT the  
26 closest to the target 0.25. Patients may eventually be treated at a dose below the dose  
27 recommended by the model for safety reasons. The patients can be recruited with no minimal time  
28 interval between successive inclusions. Two additional rules will be applied during dose escalation:  
29 no dose skipping and no escalation if at least 1 DLT is observed in the last 3 patients.  
30

31 The dose-escalation part of the study will terminate once 10 patients have been treated and  
32 evaluated at a dose currently identified as the recommended dose. Further patients will then be  
33 accrued in the expansion cohort, where toxicity data collected over the first 18-week period and DLT  
34 assessment will be analyzed approximately every 10 patients with the possibility of modification of  
35 the recommended dose, based on model-based estimates.  
36

37 The Phase II part of the study will need to include 44 patients, including the patients recruited in the  
38 dose-finding part of the phase I allocated at the dose level finally identified as the recommended  
39 dose. Thus, a minimal sample size of 47 patients will be required in this Phase I/II study (in the case  
40 of inclusion of 44 patients at dose level 2 + 3 patients at dose level 1).  
41  
42

43 **Statistical model for dose escalation**  
44

45 A one-parameter empirical power model will be used to assess the relation between the dose level  
46 and the probability of DLT:  $F(d, \alpha) = p_d^{exp(\alpha)}$  where  $F(d, \alpha)$  is the estimated probability of DLT at dose-  
47 level  $d$ ,  $p_d$  is the prior probability of DLT at dose level  $d$ , and  $\alpha$  is the unknown parameter to be  
48 estimated by the model. The vector  $\{p_{od}\}$  represent the initial guesses of toxicity probabilities,  
49 reflecting the clinicians' prior belief. The skeleton of initial guesses of toxicity probabilities  $\{p_{od}\}$  is  
50 numerically calibrated using the Lee and Cheung approach (ref ClinTrials 2009) and using the getprior  
51 function of R, ensuring good design's operating characteristics. After discussion with the clinicians,  
52 the delta defining the indifference interval was set at 0.05 ( $p(\text{DLT})=0.25 \pm 0.05$ , i.e. indifference  
53 interval: 0.20 to 0.30) and the prior MTD (MTD<sub>0</sub>) at the 2<sup>nd</sup> dose level, meaning that the clinicians  
54 believe, a priori, that the 2<sup>nd</sup> dose (6 x 6 Gy) is probably the MTD. This yields a vector of prior  
55 probabilities  $\{p_{ok}\}$  equal to 0.08, 0.16 and 0.25 for dose level -1 (5 x 5Gy), dose level 1 (5 x 6 Gy) and  
56 dose level 2 (6 x 6 Gy). The clinicians confirmed that it was in accordance with their initial guesses. A  
57 non-informative prior distribution Normal (0, 1.34) has been assigned for  $\alpha$  in the Bayesian  
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3 computation. The simulation study below confirmed that the operating characteristics and the  
4 behavior of the model defined with these parameters were reasonable.  
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### 7 **Operating characteristics:**

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

- 11 - highly toxic,
  - 12 - moderately toxic at dose levels -1 and 1, highly toxic at dose level 2
  - 13 - moderately toxic at every dose level,
  - 14 - similar with prior probabilities,
  - 15 - close to the probabilities but a little less toxic,
  - 16 - little toxic
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20 For the simulation study, we considered that the trial would recruit 47 patients, which is the minimal  
21 sample size required in this Phase I/II study.

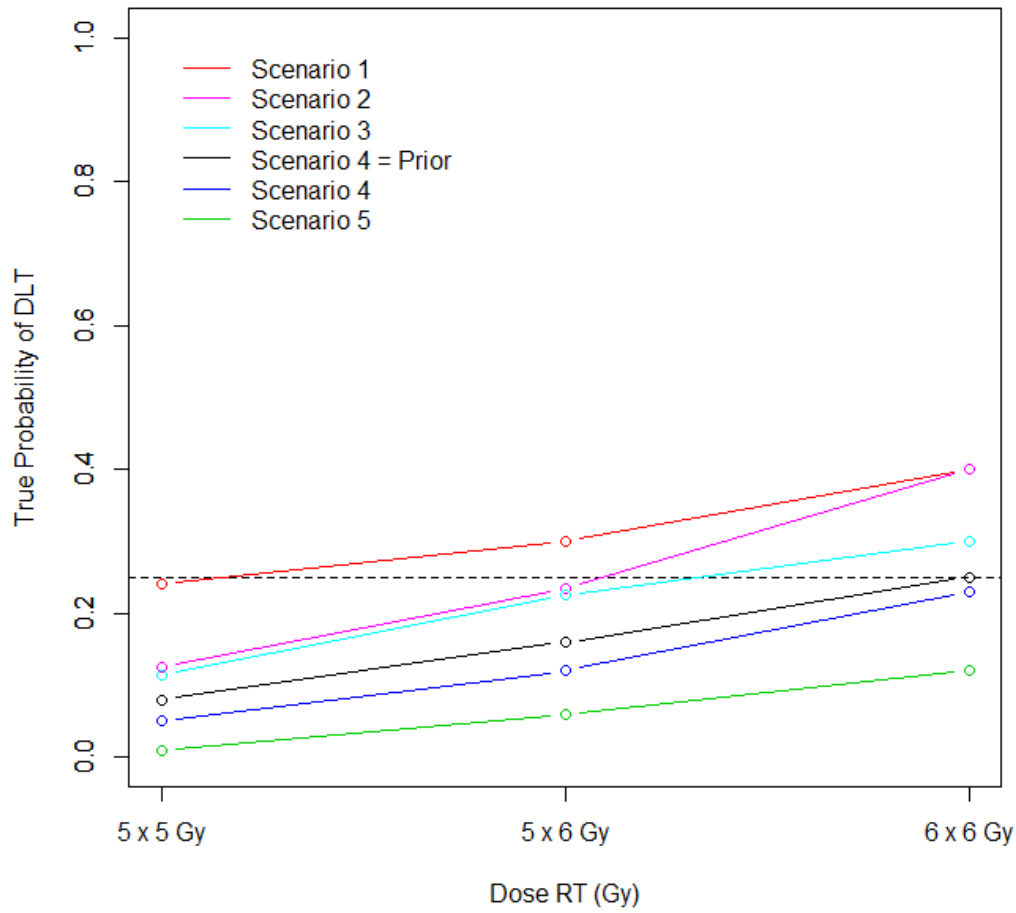
22 The following rules were implemented: no dose skipping in escalation, and no escalation if >1 DLT  
23 observed among < 3 patients.

24 For each case, 1000 trials were simulated. The Monte Carlo estimation of the percentage of dose  
25 selection, the average number of patients treated at each dose level, the average number of  
26 observed DLTs at each dose level demonstrated that the modified CRM design can efficiently identify  
27 the MTD, with a reasonable probability of overdosing, and expose few patients to toxicity.

28 A second set of simulations was performed considering a sample size of 13 patients, which is the  
29 minimal expected recruitment in the Phase I part of the study. As expected, the performance is much  
30 better when the reassessment is continued during the expansion phase (Phase II part). This is one of  
31 the advantages of the CRM method.  
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### 34 **Figure 1: Scenarios studied**

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Review only

**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
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <a href="#">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)</a>	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <a href="#">ClinicalTrials : NCT03438552</a>	2
	2b	All items from the World Health Organization Trial Registration Data Set <a href="#">IdRCB : 2017-A00008-45</a>	2
Protocol version	3	Date and version identifier <a href="#">version n°2.0 06/10/2017</a>	1
Funding	4	Sources and types of financial material, and other support <a href="#">Support by a grant of National Institute of Cancer (INCA)</a>	Not explicitly mentioned in the protocol
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <a href="#">Docteur David PASQUIER</a> <a href="#">Centre Oscar Lambret - Département de Radiothérapie</a> <a href="#">3, rue Frédéric Combemale - BP307 59020 Lille Cedex</a> <a href="#">Tél : 03.20.29.59.11 - Fax : 03.20.29.58.96</a> <a href="#">E-mail : d-pasquier@o-lambret.fr</a>	2

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2	5b	Name and contact information for the trial sponsor	1-2
3		<b>UNICANCER</b>	
4		101 Rue de Tolbiac, 75654 Paris	
5		Soazig NENAN +33 (0)185 343 113 s-	
6		nenan@unicancer.fr	
7		Meryem BRIHOUM +33 (0)1 80 50 12 95 m-	
8		brihoum@unicancer.fr	
9			
10	5c	Role of study sponsor and funders, if any, in study	46; 49
11		design; collection, management, analysis, and	
12		interpretation of data; writing of the report; and the	
13		decision to submit the report for publication, including	
14		whether they will have ultimate authority over any of	
15		these activities	
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19			
20	5d	Composition, roles, and responsibilities of the	42-44; 46
21		coordinating centre, steering committee, endpoint	
22		adjudication committee, data management team, and	
23		other individuals or groups overseeing the trial, if	
24		applicable (see Item 21a for data monitoring	
25		committee)	
26			
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31	<b>Introduction</b>		
32			
33	Background and	6a	Description of research question and justification for
34	rationale		undertaking the trial, including summary of relevant
35			studies (published and unpublished) examining
36			benefits and harms for each intervention
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40		6b	Explanation for choice of comparators
41			Not
42			applicable
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37	Objectives	7	<p>Specific objectives or hypotheses</p> <p><b>Primary objective :</b></p> <p>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.</p> <p>Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate</p> <p><b>Secondary objectives</b></p> <p>Evaluation of acute and late genitourinary toxicities of the salvage-SBRT</p> <p>Estimate the efficacy of the salvage-SBRT in terms of clinical progression-free survival and overall survival</p> <p>Evaluation of Quality of life after salvage-SBRT</p>	22-23
38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Trial design	8	<p>Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)</p> <p>Study Type: Interventional                      Primary Purpose: Treatment                      Intervention Model: Sequential Assignment                      Number of Arms: 3                      Masking: Open Label                      Endpoint Classification: Safety/Efficacy Study                      Enrollment: 47</p>	4

**Methods: Participants, interventions, and outcomes**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Study setting	9	<p>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</p> <p>Centers are hospitals and clinics (see below) :</p> <p>Centre François Baclesse, Caen, France Principal Investigator: Marlon SILVA</p> <p>Centre Jean Perrin, Clermont-Ferrand, France Principal Investigator: Geneviève LOOS</p> <p>Centre George François Leclerc, Dijon, France Principal Investigator: Gilles CREHANGE</p> <p>Centre Oscar Lambret, Lille, France Principal Investigator: David PASQUIER</p> <p>Centre Léon Bérard, Lyon, France Principal Investigator: Pascal Pommier</p> <p>Institut régional du Cancer de Montpellier, Montpellier, France Principal Investigator: David AZRIA</p> <p>Groupe Hospitalier Pitié-Salpêtrière, Paris, France Principal Investigator: Philippe MAINGON</p> <p>ICO -Site René Gauducheau, Saint-Herblain, France Principal Investigator: Stephane SUPLOT</p> <p>Institut de Cancérologie Lucien Neuwirth, Saint-Priest-en-Jarez, France Principal Investigator: Nicolas MAGNE</p>	<p>Additional form (not in the protocol)</p>
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Eligibility criteria      10	<p>Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)</p> <p>Minimum Age: 18 Years Gender: Male Accepts Healthy Volunteers?: No</p> <p><b>Inclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1. Biochemical recurrence occurring at least 2 years after external radiotherapy for prostatic adenocarcinoma by the Phoenix definition (PSA nadir + 2 ng/mL)</li> <li>2. T1-T2c and PSA <math>\leq</math>20 ng/mL and Gleason score <math>\leq</math>7 at initial diagnosis of prostate cancer before the initial/first treatment.</li> <li>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.</li> <li>4. Clinical stage T1-T2 on relapse; unilateral extracapsular extension (T3a) on MRI permitted except posteriorly relative to the rectum</li> <li>5. Estimated clinical target volume (CTV) / prostate volume &lt; 0.5 based on imaging and biopsies</li> <li>6. Pelvic and prostatic assessment by multiparametric MRI- Absence of pelvic or metastatic recurrence proven by choline PET scan</li> <li>7. Performance status WHO 0-1</li> <li>8. PSA level <math>\leq</math>10 ng/mL at baseline (before salvage-SBRT)</li> <li>9. PSA doubling time &gt;10 months</li> <li>10. International Prostate Cancer Score (IPSS) <math>\leq</math>12</li> <li>11. Uroflowmetry with a maximum flow rate &gt;10 mL/s, a postvoid residual urine volume &lt;150 mL, and a urine volume &gt;150 mL.</li> <li>12. No other anti-cancer treatment since the external radiotherapy administered as first-line treatment</li> <li>13. No other anti-cancer treatment planned for the current recurrence</li> <li>14. No contraindication to fiducial marker implants; haemostatic disorders must be corrected before implantation</li> <li>15. Age &gt;18 years</li> <li>16. Life-expectancy greater than or equal to 5 years (Lee scale)</li> <li>17. Patient registered with a health insurance system</li> <li>18. Patient who has signed the informed consent form</li> <li>19. Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests, and other study procedures indicated in the protocol.</li> </ol> <p><b>Exclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1. Lymph node or metastatic spread</li> <li>2. Late post-radiotherapy urinary or gastrointestinal toxicity of grade <math>\geq</math>2 (following primary radiotherapy)</li> <li>3. Other cancers in the last 5 years except for non-melanoma-type skin cancer</li> <li>4. History of inflammatory bowel disease</li> <li>5. Anticoagulant treatment</li> <li>6. Contraindications to undergoing MRI</li> <li>7. Prostate volume &gt;80 cc</li> <li>8. Transurethral resection of the prostate (TURP) in the 6 months before registrations</li> <li>9. Presence of rectal telangiectasia grade 3 classified by the Vienna Rectoscopy Score (obligatory rectoscopy)</li> <li>10. Previous rectal surgery</li> <li>11. Patients unable to undergo medical follow-up in the study for geographical, social or psychological</li> <li>12. Person deprived of their liberty or under protective custody or guardianship</li> </ol>	26-27
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2	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	28-30
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7		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)	31
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12			Not applicable	
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14		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	31
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18			Not applicable	
19				
20		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	31
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22			Concomitant treatment permitted : any treatment considered necessary for the health of the patient	
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25	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	23-24
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34			<b>Primary Outcome Measure:</b>	
35			[ 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.	
36			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.	
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44			[ Time Frame: 6 years ] Estimate the efficacy of the salvage-SBRT in terms of biochemical relapse-free survival rate	
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48			<b>Secondary Outcome Measure:</b>	
49			1. Time Frame: 3 years]	
50			Evaluation of acute and late genitourinary toxicities of the salvage-SBRT	
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52			2. [Time Frame: 6 years]	
53			Estimate the efficacy of the salvage-SBRT in terms of clinical progression-free survival and overall survival	
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55			3. [Time Frame: 6 years]	
56			Evaluation of Quality of life after salvage-SBRT	
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2	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
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8	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 <a href="#">At least 47 patients</a> <b>Sample Size Calculations</b>	39-40
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18	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size <a href="#">Communication and follow-up of the participating centers</a>	44; 50
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22				
23	<b>Methods: Assignment of interventions (for controlled trials)</b>			
24	Allocation:			
25				
26	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 <a href="#">TITE-CRM</a>	25; 39-40
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37	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 <a href="#">Number of inclusion attributed directly by eCRF</a>	25
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44	Implementation	16c	Who will generate the allocation sequence: <a href="#">computer/eCRF by inclusion program. Biostatistician</a> who will enrol participants: <a href="#">Investigator.</a> and who will assign participants to interventions: <a href="#">Biostatistician.</a>	25
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51	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how <a href="#">Not applicable</a>	Not applicable
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1 2 3 4 5 6 7 8 9	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial <a href="#">Not applicable</a>	Not applicable
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## 10 **Methods: Data collection, management, and analysis**

11 12 13 14 15 16 17 18 19 20 21 22 23	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 <a href="#">Describe in protocol and data management procedures</a>	30; 31-35; 43-44
24 25 26 27 28 29		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 <a href="#">Describe in protocol and data management procedures</a>	31; 31-35
30 31 32 33 34 35 36 37 38 39	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 <a href="#">Describe in protocol and data management procedures</a>	30; 43-44
40 41 42 43 44 45 46 47 48 49 50	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
51 52 53 54 55 56 57		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) <a href="#">Not applicable</a>	41-42
58 59 60		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) <a href="#">Not applicable</a>	41-42

## 58 **Methods: Monitoring**

1				
2	Data monitoring	21a	Composition of data monitoring committee (DMC);	42
3			summary of its role and reporting structure; statement	
4			of whether it is independent from the sponsor and	
5			competing interests; and reference to where further	
6			details about its charter can be found, if not in the	
7			protocol. Alternatively, an explanation of why a DMC	
8			is not needed	
9				
10			<a href="#">Coordinator : validate the risk analysis (LIR) and the</a>	
11			<a href="#">monitoring plan</a>	
12				
13			<a href="#">Project Manager : determine the risk analysis (LIR) and</a>	
14			<a href="#">write the monitoring plan</a>	
15				
16			<a href="#">Clinical Research Associate (CRA) :perform monitoring</a>	
17			<a href="#">according the monitoring plan</a>	
18				
19		21b	Description of any interim analyses and stopping	42
20			guidelines, including who will have access to these	
21			interim results and make the final decision to	
22			terminate the trial	
23				
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25	Harms	22	Plans for collecting, assessing, reporting, and	35-38
26			managing solicited and spontaneously reported	
27			adverse events and other unintended effects of trial	
28			interventions or trial conduct	
29				
30			<a href="#">This point is provided by the vigilance unit of the sponsor.</a>	
31			<a href="#">All details are described in the protocol</a>	
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34	Auditing	23	Frequency and procedures for auditing trial conduct, if	44
35			any, and whether the process will be independent	
36			from investigators and the sponsor	
37				
38			<a href="#">Actually and according the risk analysis, no audit is planned</a>	
39				
40	<b>Ethics and dissemination</b>			
41				
42	Research ethics	24	Plans for seeking research ethics	45
43	approval		committee/institutional review board (REC/IRB)	
44			approval	
45			<a href="#">N° IdRCB : 2017-A00008-45</a>	
46				
47				
48			<a href="#">Initial Approval by CPP Nord-Ouest I (Committee for the</a>	
49			<a href="#">Protection of Personnes/Ethic committee) : 25/07/2017</a>	
50			<a href="#">Approval Number: CPP3517-I</a>	
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2	Protocol	25	Plans for communicating important protocol	46
3	amendments		modifications (eg, changes to eligibility criteria,	
4			outcomes, analyses) to relevant parties (eg,	
5			investigators, REC/IRBs, trial participants, trial	
6			registries, journals, regulators)	
7			<a href="#">Each major protocol amendment is submitted to authorities</a>	
8			<a href="#">for approval.</a>	
9			<a href="#">After approval, it is communicated to all the actors of this</a>	
10			<a href="#">project (investigators, trial centers, trial registry ....)</a>	
11				
12				
13	Consent or assent	26a	Who will obtain informed consent or assent from	47
14			potential trial participants or authorised surrogates,	
15			and how (see Item 32)	
16			<a href="#">Principal Investigator or sub-investigator</a>	
17				
18		26b	Additional consent provisions for collection and use of	33; 38; 48
19			participant data and biological specimens in ancillary	
20			studies, if applicable	
21			<a href="#">Not applicable</a>	
22				
23				
24	Confidentiality	27	How personal information about potential and enrolled	43; 47-49
25			participants will be collected, shared, and maintained	
26			in order to protect confidentiality before, during, and	
27			after the trial	
28			<a href="#">Collected by investigators and CRA on each trial centers.</a>	
29			<a href="#">These data are anonymized.</a>	
30			<a href="#">Shared on the eCRF.</a>	
31			<a href="#">There is a control access on the eCRF</a>	
32				
33				
34				
35	Declaration of	28	Financial and other competing interests for principal	Not
36	interests		investigators for the overall trial and each study site	applicable
37			<a href="#">None</a>	
38				
39	Access to data	29	Statement of who will have access to the final trial	48-49
40			dataset, and disclosure of contractual agreements	
41			that limit such access for investigators	
42			<a href="#">Directly on the eCRF</a>	
43				
44				
45	Ancillary and post-	30	Provisions, if any, for ancillary and post-trial care, and	Not
46	trial care		for compensation to those who suffer harm from trial	applicable
47			participation	
48			<a href="#">Not applicable</a>	
49				
50				
51	Dissemination	31a	Plans for investigators and sponsor to communicate	50
52	policy		trial results to participants, healthcare professionals,	
53			the public, and other relevant groups (eg, via	
54			publication, reporting in results databases, or other	
55			data sharing arrangements), including any publication	
56			restrictions	
57				
58				
59			<a href="#">A publication is planned; no publication restriction.</a>	
60				

1 2 3 4 5 6 7 8 9	31b	Authorship eligibility guidelines and any intended use of professional writers	50
		Coordinator will be the first author; co investigators will be authors.	
10 11 12 13 14 15	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
		N/A	

## Appendices

16 17 18 19 20 21 22 23 24 25 26 27 28 29	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional form (not in the protocol)
24 25 26 27 28 29	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 <a href="#">Not applicable</a>	59

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\*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.