Randomized phase II study evaluating late toxicity following Intensity-Modulated Radiotherapy and two Image-Guided strategies with corresponding treatment margins.
RCMIGI

ID-RCB n°: 2015-A00817-42
Sponsor Code: ICM-URC 2015/33

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TITLE	**Randomized phase II study evaluating late toxicity following Intensity-Modulated Radiotherapy and two Image-Guided strategies with corresponding treatment margins**
PROTOCOL CODES	**Acronym**: RCMIGI **Sponsor Code**: ICM-URC 2015/33 **ID-RCB number:** 2015-A00817-42
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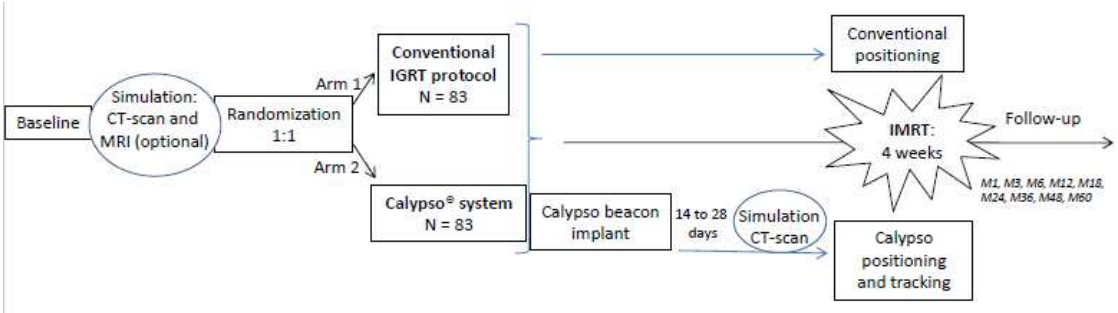
BACKGROUND AND **AND RATIONALE**	Prostate cancer is the most frequent cancer in men. Radiotherapy is one of the reference treatments for localized prostate cancer. Prostate was initially thought to be a non-moving target, but the newest reports have raised the contrary as evidence. Image-guided radiotherapy (IGRT) is a current standard treatment for localized prostate cancer which enables to take into account interfractional prostate motion before treatment.

	The Calypso® System (Varian Medical Systems, Inc., Palo Alto, CA) is a recent technology using electromagnetic transponders implanted within the prostate. It is a real-time target tracking system that takes into account both inter- and intrafractional target motion. So the exact position and movement of the prostate can be determined during radiation therapy treatment. As Planned Target Volume (PTV) margins integrate set-up margins and the management of organ motion, margin reduction can reasonably be considered in case of target motion management improvement. To date, no prospective randomized clinical data is available using this technique for the treatment of low- or intermediate-risk prostate cancer patients with modern standard fractionation radiotherapy and image guidance. The aim of this study is to assess pelvic late toxicity rate after intensity- modulated radiotherapy (IMRT) when using the Calypso® System with a reduction of treatment margins. In this randomized study, patients will receive IGRT treatment using the Calypso system or a conventional IGRT treatment.
STUDY OBJECTIVE(S)	**<u>Primary objective</u>** The main objective of the study is to assess the late pelvic toxicity rate after intensity-modulated radiotherapy (IMRT) when using the Calypso® System with a reduction of the treatment margins. **<u>Secondary objectives</u>** The secondary objectives are to assess: - any acute toxicity, - any other late toxicity, - biochemical control, - complication relapse-free survival (CRFS), - quality of life, - correlation between late toxicities and the radiation-induced T- lymphocyte apoptosis (RILA) rate.
STUDY DESIGN	Open, prospective, monocentric, randomized, phase II clinical trial.
INVESTIGATIONAL SITE	One investigator center will participate in the study: Montpellier Cancer Institute (ICM).
ELIGIBILITY CRITERIA	**i) <u>Inclusion criteria</u>** - Localized prostate cancer, histologically proven. - No evidence of metastases (M0). - No evidence of lymph nodes involvement (N0) (bilateral lymph node dissection is not mandatory if lymph node involvement risk is low according to the Partin tables). - Low-risk or intermediate clinical stage according to the D'Amico classification (T1-T2 and Gleason < 8 and PSA < 20 ng/ml) (appendix 3). - No grade ≥ 2 urinary or rectal clinical sign or symptom according to the CTCAE V4.03 scale. - Performance status ECOG ≤ 1. - No hip prosthesis or metallic vascular graft near the prostate. - No endopenian stent. - No pace maker, implanted defibrillator or neurostimulator. - No allergy to local anesthetics. - No irreversible anticoagulation or antiplatelet treatment for the implantation period.

	- Pelvic and abdominal anatomy compatible with the use of the Calypso® system (predictive detector to fiducials distance less than 19 cm, evaluated on planning CT-scan) (distance from skin surface to prostate center less than 17 cm. Furthermore, it is necessary to make sure that the patient's anatomy allows the positioning of the receiver over 30 cms, in a cranio-caudal manner, on both sides of the isocentre position. - Patient aged ≥ 18 and less than 80 years old. - Dated and signed written informed consent available. - Patients must be affiliated to a French Social Security System. **ii) Exclusion criteria** - Indication of pelvic nodes irradiation. - Prior pelvic irradiation. - Biopsy-proven seminal vesicle invasion. - Prior bilateral orchiectomy. - Prior radical prostatectomy. - Other malignancy except adequately-treated basal cell carcinoma of the skin or other malignancy from which the patient has been disease-free for at least 5 years. - Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial. - Other uncontrolled systemic disease (cardiovascular, renal, liver, pulmonary embolism, etc.). - Known VIH positive patients (no specific test needed). - Known homozygote ATM Mutation (Ataxia telengiectasia).
TREATMENT MODALITIES	Two image guided strategies during intensity-modulated radiotherapy in the treatment of localized prostate cancer will be considered: **Arm 1 : (control) :** Image-guided radiation therapy (IGRT) with standard margins **Arm 2** : Calypso tracking system with margin reduction The control arm (arm 1) will represent an internal control to validate the hypothesis of the Fleming design used for calculation of the sample size.  Registration and randomization will be performed at the Biometrics Unit of the Montpellier Cancer Institute (France).

STUDY ENDPOINTS	**<u>Primary endpoint</u>:** The primary endpoint is defined by the incidence of grade ≥ 2 late pelvic toxicities between 3 months and 2 years after radiation period (based on the Common Terminology Criteria for Adverse Events Version 4.03). **<u>Secondary endpoints</u>:** The secondary endpoints include: Any acute toxicity (until 3 months post radiotherapy) Any late toxicity (between 3 months and 2 years post radiotherapy), Biochemical relapse-free survival (BRFS) at 5 years is assessed by PSA tests: PSA nadir + 2, Complication relapse-free survival (CRFS) (at 2 years)**,** Complication relapse-free survival (CRFS) (at 5 years)**,** Quality of life evaluation using EORTC QLQ-C30 and QLQ-PR25 questionnaires, Specific questionnaires for urinary obstruction (International Prostate Symptom Score: IPSS) and for erectile function (International Index of Erectile Function: IIEF5), Correlation between late toxicities (between 3 months and 2 years post radiotherapy) and the radiation-induced T-lymphocyte apoptosis (RILA) rate (low (≤15) versus high (>15)).
SAMPLE SIZE	The primary endpoint of this study is the **incidence of late pelvic grade ≥ 2 toxicities.** Sample size calculation for the experimental arm (Calypso system) will be based on a single-stage Fleming design for phase II trials. Fleming design is formulated in terms of success rate. In the context of this study, we define a success as a patient **without grade ≥ 2 late pelvic toxicity occurring** after 3 months and until 2 years after treatment (based on the Common Terminology Criteria for Adverse Events Version 4.03). Considering that the common expected success rate in this indication is 85% (p0), the smallest success rate expected in the experimental arm is set at 95% (p1). Using a one-stage Fleming design with one-sided α=0.05 and β=0.10, it will be necessary to include 75 evaluable patients.

<table>
<tr><td></td><td>
The experimental treatment (Calypso system) may be considered sufficiently safe if at least 69 patients (among 75 evaluable patients) show a treatment success, otherwise the Calypso system will be considered as insufficiently safe.
<table>
<tr><th>Stage</th><th>Nb.of patients</th><th>Insufficiently active safe if</th><th>Sufficiently active safe if</th></tr>
<tr><td>1</td><td>75 first evaluable patients</td><td>≤ 68 successes</td><td>≥ 69 successes</td></tr>
</table>
A concurrent control arm of a size equal to half that experimental, that is 38 patients, will be included in the study using a 2:1 randomization ratio (Calypso : Control).

Taking into account a 10% rate of non-evaluable patients, a total of 83 patients will be required in CALYPSO arm whereas 42 patients in Control arm.

Accordingly, a total of 125 patients will be recruited in the trial, 83 and 42 patients in Calypso and Control (IGRT) arms respectively.

Randomisation will be stratified according to the:
Radiation-induced lymphocyte apoptosis (RILA) test (low (≤15) versus high (>15)),
Indication for hormonotherapy (yes versus no),
Anticoagulation treatment (yes versus no),
Diabetes patient status (yes versus no)
</td></tr>
<tr><td>STUDY PERIOD</td><td>
- Study start date: April 2016
- Planned enrolment duration: 120 months
- Study completion date: December 2028(12 years)
</td></tr>
</table>

LIST OF ABREVIATIONS

ADL	Activities of Daily Living
Ae	Adverse Event
Aes	Adverse Events
AP	Abdomino-Pelvic
ATM	Ataxia Telangiectasia Mutated
BRFS	Biochemical Relapse-Free Survival
CBCT	Cone-beam Computed Tomography
CI	Confidence Interval
CRF	Case Report Form
CRFS	Complication Relapse-Free Survival
CT	Computed Tomography
CTV	Clinical Target Volume
Gy	Gray
IGRT	Image-Guided Radiation Therapy
IIEF5	International Index of Erectile Function
IMRT	Intensity-Modulated Radiotherapy
IPSS	International Prostate Symptom Score
ITT	Intent-To-Treat
LH-RH	Luteinizing Hormone - Releasing Hormone
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OBI	On-Board Imager
PTV	Planned Target Volume
PP	Per-Protocol
RCMI	Radiothérapie Conformationnelle avec Modulation d'Intensité
RCMIGI	Radiothérapie Conformationnelle avec Modulation d'Intensité Guidée par l'Image
RILA	Radiation-Induced Lymphocyte Apoptosis
RT	Radiotherapy
RTGI	Radiothérapie Guidée par l'Image
SAP	Statistical Analysis Plan

1. Background and Rationale

1.1. RADIOTHERAPY FOR PROTATE CANCER

Prostate cancer is the most frequent cancer in men [1]. Radiotherapy is one of the reference treatments for localized prostate cancer [2]. The results of radiotherapy versus surgery (radical prostatectomy) are modulated by the patients' prognostic factors, and are considered equivalent [3]. Most patients survive for many years following external beam radiotherapy (RT) for non-metastatic prostate cancer and are therefore at risk of late treatment sequelae. The favorable outcomes after radiotherapy for prostate cancer allows treated patients to be considered as long-term survivors. They are thus exposed to the possibility of late secondary effects, negatively impacting their quality of life. The expected main late toxicities after prostate radiotherapy are mainly digestive, urinary and sexual toxicities. For prostate-only radiotherapy (without pelvic irradiation), digestive toxicities are only rectal: proctitis, rectal bleeding, rectal pain, rectal stenosis, rectal mucositis and diarrhea. Urinary toxicities are related to bladder and urethra radiotherapy, and are mainly cystitis, dysuria, pollakiuria, nycturia, hematuria, uretral stenosis, urine incontinence, urinary urgencies, urinary tract obstruction, urinary tract pain. Expected late sexual toxicities are erectile dysfunction and ejaculation disorders [4–6].

Many factors influence the occurrence of these toxicities, including the treated volume, total dose, fractionation and patient radiosensitivity [7, 8]. The reduction of the treatment margins, when safely possible, might thus improve the toxicity profile of radiotherapy by reducing the treatment volume.

In 2014-2015, when the protocol was written, dose-escalated normo-fractionated external beam radiotherapy (EBRT) was a standard of care for low to intermediate risk prostate cancer. That's why a standard fractionation of 2 Gy x 40 fractions was chosen for the first years of inclusion.
However, since then, the results of major studies of moderate hypofractionation EBRT have been released.
In 2016, 2 non inferiority trials and 1 superiority trial were published [9].
The CHHiP trial was a large 3 arms trial establishing that moderate hypofractionation of 3 gy x 20 fractions was non inferior to normo fractionated EBRT in terms of biochemical and clinical control [10].
The RTOG 0415 trial confirmed that moderate hypofractionation was non inferior to normofractionation regarding cancer control (5-year DFS) [11].
However, the HYPRO trial failed to demonstrate that moderate hypofractionation was superior to dose-escalated normo fractionated EBRT with respect to 5-year relapse-free survival [12].
In 2017, 2 additional trials of moderate hypofractionation for prostate cancer were published [9].
The Regina Elena National Cancer Institute trial did not demonstrate a superiority of 62 Gy given in 3.1 Gy fractions over 80 Gy normo fractionated trial for cancer control. However, overall toxicity was similar between the 2 arms [13].
The PROFIT trial established that moderate hypofractionation was non inferior to dose-escalated 78 Gy normo fractionated EBRT regarding biochemical-clinical failure [14].
When looking to CHHiP and PROFIT trial, probably the best and largest trials on moderate hypofractionation for prostate cancer, late pelvic toxicity was not significantly different in hypofractionated Vs normofractionated arms.

On the basis of these results, moderate hypofractionated EBRT has been gradually adopted as an attractive therapeutic option for the treatment of low and intermediate risk prostate cancer patients. Without calling into question the interest of dose-escalated normo fractionated radiotherapy, moderate hypofractionation also has the advantage of reducing treatment time by half, which simplifies patient care.
EAU-EANM-ESTRO-ESUR-SIOG 2020 guidelines has endorsed moderate hypofractionation has a standard of care [15].
ESTRO-GIRO recently published a survey on hypofractionation which confirmed that hypofractionation was widely adopted by the radiotherapy community for the treatment of low to intermediate risk prostate cancer. Indeed, more than 60 % of EBRT for this cancer type in Europe and 80 to 90 % in Northern America were treated with hypofractionation [16].
As our center has a good experience of moderate hypofractionation of 3.1 Gy x 20 fractions, we propose to switch to this fractionation for the remaining patients to include in the study [17].

1.2. IMAGE-GUIDED RADIOTHERAPY (IGRT)

Organ motion is a recent concern during prostate radiotherapy. Prostate was initially thought to be a non-moving target, but newest reports have raised the contrary as an evidence [18, 19]. Image-guided radiotherapy (IGRT) is a current standard treatment for localized prostate cancer which enables taking into account interfractional prostate motion before treatment [20-22]. Few systems have been developed to account for intrafractional target motion [23-27]. The newest linear accelerators for example are able to use kilovoltage images of the on-board imager (OBI) to check for the intrafractional fiducials position at several time points during radiotherapy delivery.

IGRT protocols in use are highly variable depending of in-house policies at the different hospitals and imaging capabilities of the linear accelerators available [22, 26]. No consensual guidelines regarding IGRT for prostate cancer IMRT are available. A minimal requiring for accordance to the definition is to provide at least daily imaging. Some protocols use fiducial implants to improve repositioning, others tridimensional on-board imaging, but the optimal protocol remains to be defined [28].

1.3. CALYPSO® SYSTEM

The Calypso® System (Varian Medical Systems, Inc., Palo Alto, CA) is a real-time target tracking system that takes into account both inter- and intrafractional target motion [19]. This system consists in an electromagnetic array that can continuously detect, with sub-millimeter accuracy, the positions of signal-emitting transponders implanted in the target [29, 30]. It was shown to be more accurate than on-board imaging repositioning in observational prospective and retrospective studies [27, 29, 31]. Electromagnetic positioning seems to be the most precise system for real-time monitoring and inter/intra fractional prostate motion prediction as compared with setup using skin marks or stereoscopic X-ray localization of fiducials [27, 32, 33].

As Planned Target Volume (PTV) margins integrate set-up margins and the management of organ motion, the reduction of the treatment margins can reasonably be considered in case of target motion management improvement.

The system was recently analyzed in feasibility studies in a limited number of patients [19, 30, 34-37], and in a phase II study assessing stereotactic ablative body radiotherapy in low-risk prostate cancer patients [38]. One cohort study retrospectively compared a margin

reduction cohort using the Calypso® System with a conventional-margin cohort in terms of acute morbidity in prostate cancer patients treated with high-dose IMRT [39].

To date, no prospective randomized clinical data is available using the Calypso technique for the treatment of low- or intermediate-risk prostate cancer patients with modern standard fractionation radiotherapy and image guidance.

Whether margin reduction could be translated into an improved toxicity rate with equal efficacy is an important question to be answered before widespread clinical implementation of the technique.

1.4. HYPOTHESIS

The tolerance profiles could be different between the conventional IGRT protocol and the IGRT protocol using the Calypso® System in patients with low- or intermediate-risk prostate cancer. The Calypso® System takes into account the target motion of the prostate and could reduce the margins. This would result in improving the pelvic toxicity rate with the same treatment efficiency.

We hypothesize that the rate of grade ≥ 2 pelvic toxicities will be ≤ 5% with the use of the Calypso system. The results obtained will allow an assessment of the Calypso system in terms of late pelvic toxicities.

2. Study design

2.1. TRIAL DESIGN

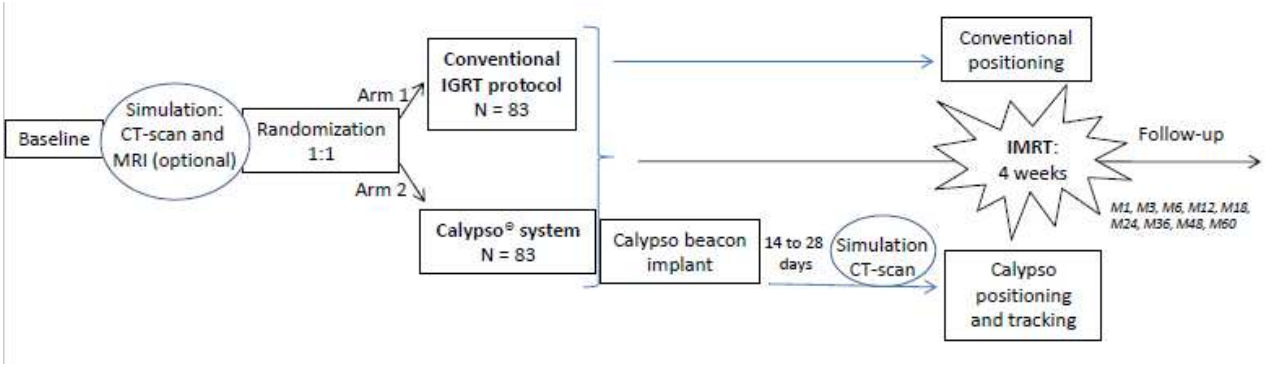
This trial is a phase II, monocentric, open-label, two- arm and randomized study using two-image guided strategies during intensity-modulated radiotherapy treatment: IGRT with standard margins (Arm 1) and the Calypso tracking system with margin reduction (Arm 2) in the treatment of localized prostate cancer.

The Control arm will represent an internal control to validate the hypothesis of the Fleming desing used for calculation of the sample size.

A total of 113 evaluable patients (125 patients if we consider a 10% of non-evaluable patients) will be randomized into arms 1 and arm 2 in a 2:1 ratio.

Arm 1: IGRT arm with standard margins (38 evaluable patients)

Arm 2: Calypso® arm with margin reduction (75 evaluable patients)



Randomization 2:1 will be stratified according to the:

- Radiation-induced lymphocyte apoptosis (RILA) test (low (≤ 15) versus high (>15)) [40, 41],
- Indication for hormonotherapy (yes versus no),
- Anticoagulation treatment (yes versus no),
- Diabetes patient status (yes versus no)

2.2. ESTIMATED STUDY DURATION

The subject accrual period is planned to last approximately 60 months.

- Submission to the Ethics committee : December 2015
- Start of inclusions : April 2016
- End of inclusions : April 2026
- Statistical analysis-: December 2028

3. Trial objectives

3.1. PRIMARY OBJECTIVE

The main objective of the study is to assess the late pelvic toxicity rate after intensity-modulated radiotherapy (IMRT) when using the Calypso® System with a reduction of the treatment margins.

3.2. SECONDARY OBJECTIVES

The secondary objectives are to assess:

- any acute toxicity,
- any other late toxicity,
- biochemical control,
- complication relapse-free survival (CRFS),
- quality of life,
- correlation between late toxicities and the radiation-induced T-lymphocyte apoptosis (RILA) rate.

4. Patient selection

Each patient should meet all of the inclusion criteria (Section 4.1) and none of the non-inclusion criteria (Section 4.2), for this study.

4.1. INCLUSION CRITERIA

The patients must fulfill all the following criteria to be eligible to enter the study:

- Localized prostate cancer, histologically proven.
- No evidence of metastases (M0).
- No evidence of lymph nodes involvement (N0) (bilateral lymph node dissection is not mandatory if lymph node involvement risk is low according to the Partin tables).
- Low-risk or intermediate clinical stage according to the D'Amico classification (T1-T2 and Gleason < 8 and PSA < 20 ng/ml) (appendix 3).
- No grade ≥ 2 urinary or rectal clinical sign or symptom according to the CTCAE V4.03 scale.
- Performance status ECOG ≤ 1.
- No hip prosthesis or metallic vascular graft near the prostate.
- No endopenian stent.
- No pace maker, implanted defibrillator or neurostimulator.
- No allergy to local anesthetics.
- No irreversible anticoagulation or antiplatelet treatment for the implantation period.
- Pelvic and abdominal anatomy compatible with the use of the Calypso® system (predictive detector to fiducials distance less than 19 cm, evaluated on planning CT-scan) (distance from skin surface to prostate center less than 17 cm. Furthermore, it is necessary to make sure that the patient's anatomy allows the positioning of the receiver over 30 cms, in a cranio-caudal manner, on both sides of the isocentre position.
- Patient aged ≥ 18 and less than 80 years old.
- Dated and signed written informed consent available.
- Patients must be affiliated to a Social Security System.

4.2. NON-INCLUSION CRITERIA

Patients presenting with any of the following non-inclusion criteria will not be included in the study:

- Indication of pelvic nodes irradiation.
- Prior pelvic irradiation.
- Biopsy-proven seminal vesicle invasion.
- Prior bilateral orchiectomy.
- Prior radical prostatectomy.
- Other malignancy except adequately-treated basal cell carcinoma of the skin or other malignancy from which the patient has been disease-free for at least 5 years.
- Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.
- Other uncontrolled systemic disease (cardiovascular, renal, liver, pulmonary embolism, etc.).
- Known VIH positive patients (no specific test needed).
- Known homozygote ATM Mutation (Ataxia telengiectasia).

4.3. PATIENT ENROLMENT AND REGISTRATION

Enrolment in the study is defined as both the signing of the Informed Consent and validation of eligibility criteria by the investigator. The inclusion and exclusion criteria should be checked during the screening period to ensure appropriate subjects are assigned to participate in the present study.
Eligible patients will be randomized prior to starting therapy.

Randomization will be stratified by following factors:

- RILA test (low (≤ 15) versus high (>15)) ,
- Indication for hormonotherapy (yes versus no),
- Anticoagulation treatment (yes versus no),
- Diabetes patient status (yes versus no)

Registration and randomisation will be performed at the Biometrics Unit of the Montpellier Cancer Institute (France).

Investigators should use a dedicated registration form (see appendix 4) inserted into the CRF and fax the filled and signed form to:

Biometrics Unit – Montpellier Cancer Institute (Montpellier)
From Monday through Friday (9.00 AM to 5.00 PM)
Fax: +33 4 67 61 37 18
Phone: +33 4 67 61 45 40 / 45 48

Afterward, the investigator will receive by fax the notification form with the patient's identification number be reported on each CRF page and the treatment arm assigned (either IGRT with standard margins or Calypso with margin reduction).

5. Treatments

5.1. PATIENT WORKFLOW FOR IMPLANT AND SIMULATION

Patients will undergo Computed Tomography (CT) scan based and Magnetic Resonance Imaging based (optional) virtual simulations before fiducial implants in order to enhance target volume accuracy.

They will then undergo a Calypso beacon implant (arm 2) according to the treatment arm allocation (see appendix 5 for the implantation instructions). The Calypso beacon implant will be performed at the Beau Soleil Clinic Urology Department (Montpellier).

Arm 2: patients will undergo a second CT-scan simulation 14 to 28 days after the implant for radiotherapy planning. The radiotherapy will be performed 3 to 6 weeks after the implantation.

5.2. CONTOURING

Organs

Prostate has to be defined as Clinical target Volume (CTV). Seminal vesicles will be delineated in their proximal part, i.e. 2 cm from their prostate attachment in the cranio- caudal and lateral directions. Rectum is defined 2 cm upper and lower the CTV1. The bladder should be

drawn on each slide where it appears. Femoral heads are defined from the head of the acetabulum to the trochanter.

Planning volumes

CTV1 = prostate + seminal vesicles

CTV2 = prostate

- ARM 1:
  - PTV1 = CTV1 + 1cm (0.5 cm in the posterior direction)
  - PTV2 = CTV2 + 1cm (0.5 cm in the posterior direction)
  - PTV2 $_{3mm}$ = CTV2 + 0.3 cm
- ARM 2:
  - PTV1 = PTV2 + [VS+ (1 cm cranial, 1 cm lateral, 0.3 cm anterior and 0.5 cm posterior)]
  - PTV2 $_{3mm}$ = CTV2 + 0.3 cm

Dose constraints

ARM 1: IGRT arm with standard margins

PTV2: 95% of the volume covered by the 95% prescription dose (59 Gy).
D 99% ≥ 90% of the prescribed dose (55,8 Gy), D 107% ≤ 2% of volume, Dmax (0.1%)<110%

PTV1: 95% of the volume covered by the 95% prescription dose (42 Gy)

Rectum: Dose 0.1% ≤ 62 Gy (59 Gy if possible),
V53 Gy ≤ 50%
Bladder: D0.1% ≤ 63 Gy.
V53 Gy ≤ 50%

ARM 2: Calypso® arm with margin reduction

PTV2:
D 99.5% (99% accepted) of the volume ≥ 95% prescription dose 59 gy.
V 100 % of the prescribed dose (62 Gy) ≥90% PTV2

PTV1:
D 99.5% (99% accepted) ≥ 95% prescription dose 42 Gy
V 100 % of the prescribed dose (‘’ Gy) ≥90% PTV1

Rectum: Dose 0.1% ≤ 62 Gy (59 Gy if possible), V53 Gy ≤ 50%
Bladder: D0.1% ≤ 63 Gy. V53 Gy ≤ 50%

5.3. DOSE PRESCRIPTION

62 Gy will be delivered to the PTV2 for patients in arm 1 and PTV2 3mm for patients in arm 2, and 44 Gy to the PTV1 for patients in both arms in 20 fractions.

The period treatment will be of 4 weeks.

5.4. BEAM DELIVERY

All treatment will be delivered with Volumetric Modulated Arc therapy using 2 arcs.

5.5. PATIENT SETUP AND VERIFICATION

Arm 1: CBCT and kV-kV positioning + per-fraction verification with kV imaging each 90° of rotation and gating with True Beam V2.0.

Arm 2: CBCT and Calypso positioning + calypso per-treatment tracking.

5.6. CONCOMITANT ANDROGEN DEPRIVATION

Concomitant hormonotherapy using 3 to 6 months Luteinizing Hormone – Releasing Hormone (LH-RH) agonists will be used in intermediate-risk patients unless medical contra- indication, according to the standard practice.

6. Expected Adverse events

Adverse events (AEs) will be assessed according to the NCI-CTCAE v4.03 toxicity scale (see appendix 2).

The most frequent AEs due to the beacon implant are:

- Bleeding (hematuria, hematospermia, hematochezia),
- Pain (procedural, anal, perineal, bowel movements, unspecified),
- Dysuria,
- Infection (urinary tract infection with prostate infection which occur in <2% of patients),
- Fever.

Other observed AEs include:

- Urinary retention,
- Urinary obstructive symptoms (urinary frequency, weak stream, etc.),
- Implant migration.

The following AEs also have been documented following transrectal biopsy; however, they occur in <1% of patients:

- Nausea or sickness
- Allergic reaction to antibiotic prophylaxis
- Perineal swelling
- Sepsis
- Epididymitis
- Temporary fecal incontinence
- Urethral perforation
- Deep venous thrombosis
- Vascular embolization of the implant (pulmonary embolism)
- Vasovagal episode
- Cardiac arrhythmia

Expected acute AEs due to the radiotherapy are:

- Moderate fatigue,
- An increase in the frequency of urination and defecation,
- Rectal burning sensation with sometimes hemorrhoids crisis,
- Increased frequency to defecate without exoneration of stools.

Expected late AEs due to the radiotherapy are:

- Difficulty to urinate,
- An increase in the frequency of urination and defecation,
- Rectal or bladder bleeding
- Sexual difficulties.

The decision to discontinue radiotherapy due to inacceptable toxicity will be taken in agreement with the coordinator and the investigator.

7. Study plan and timing procedures

7.1. FLOW CHART OF THE STUDY

		Baseline	Before radiotherapy	During Radiotherapy	End of radiotherapy	Follow-up (from end of radiotherapy)								
						M1	M3	M6	M12	M18	M24	M36	M48	M60
Signed informed consent form[1]		+												
Review of eligibility criteria		+												
Demographic information		+												
Medical, surgical and oncologic history[2]		+												
Height[3], Weight		+												
ECOG performance status		+												
Clinical examination		+			+	+	+	+	+	+	+	+	+	+
Toxicity evaluation (CTCAE V4.03)		+	+[4]	+	+	+	+	+	+	+	+	+	+	+
Pelvic MRI or AP CT-scan[4 5]		+												
Bone scan or whole-body bone MRI[6]		+												
PSA test		+				+	+	+	+	+	+	+	+	+
Before randomization	Simulation CT-scan (optional MRI)	+												
After randomization	Arm 1: Conventional IGRT[7]		+	Conventional positioning										
	Arm 2: Calypso beacon implant[8] Simulation CT-scan[9]		+	Calypso positioning and tracking										
RILA test		+												
Quality of life EORTC questionnaires QLQ-C30 and QLQ-PR25[0]		+			+	+	+	+	+	+	+	+	+	+
IPPS and IIEF5 questionnaires[11]		+			+	+	+	+	+	+	+	+	+	+

[1] **Signed informed consent form**: prior to any study procedures
[2] **Medical, surgical and oncologic history**: including cancer diagnosis, prior surgery, concurrent illness, concomitant treatment.
[3] **Height**: only at baseline.
[4] **Toxicity evaluation (CTCAE V4.03)**: if the patient is randomly assigned to the arm 2 then the toxicity evaluation (including urinary, rectal and sexual symptoms) will be performed before and after the Calypso beacon implant.
[5, 6] **Pelvic magnetic resonance imaging (MRI) or abdomino-pelvic (AP) CT-scan and Bone scan or whole-body bone MRI** are required for the intermediate clinical stage. **AP CT-scan and Bone scan or whole-body bone MRI** are left at the investigator's discretion for the low-risk clinical stage.
During and after the treatment radiologic procedures are left at the investigator's discretion.
[7] **Conventional IGRT** if the patient is randomly assigned to the arm 1.
[8] **Calypso beacon implant** if the patient is randomly assigned to the arm 2.
[9] **Simulation CT-scan** if the patient is randomly assigned to the arm 2: will be performed 14 to 28 days after the implant for radiotherapy planning.
[10, 11] **Quality of life evaluation** using questionnaires will be performed before and at the end of treatment and at each evaluation (1 month, 3 months, every 6 months until two years then every year from end of radiotherapy)**.**
[11] **International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF5).**

7.2. CLINICAL EVALUATION AND FOLLOW-UP PROCEDURES

7.2.1. BASELINE

The following procedures and assessments will be performed before any treatment:
The patient must provide a signed informed consent form prior to any study related procedures.

- Review of eligibility criteria (medical, surgical and cancer histories),
- Demographic information,
- Medical, surgical and oncologic history including cancer diagnosis, prior surgery, concurrent illness, concomitant treatment:
  - Concurrent illness: diabetes*,
  - indication for hormonotherapy*,
  - Anticoagulant treatment*,
- Height, weight,
- ECOG performance status (appendix 1),
- Clinical examination,
- Toxicity evaluation,
- Pelvic MRI or AP CT-Scan within 4 months prior to starting treatment,
- Bone scan or whole-body bone MRI within 4 months prior to starting treatment,
- PSA test,
- RILA test (see paragraph 9)*,
- Quality of life using QLQ-C30 (appendix 10) and QLQ-PR25 (appendix 11) questionnaires [42],
- IPPS (appendix 12) and IIEF5 (appendix 13) questionnaires [43].

* Those procedures are required for randomization.

The RILA test will be performed during the first consultation or at the time of simulation CT-scan visit and after signed informed consent form.

Before randomization, a simulation CT-scan (optional MRI) will be performed.
A consultation with an anesthetist will be planned in order to perform the Calypso beacon implant. According to the randomization result, the consultation will be only performed in the Calypso arm (arm 2) and cancelled in the arm 1.

7.2.2. BEFORE RADIOTHERAPY (AFTER RANDOMIZATION)

- Conventional IGRT protocol if the patient is randomly assigned to the arm 1.
- Calypso beacon implant if the patient is randomly assigned to the arm 2. The toxicity evaluation (including urinary, rectal and sexual symptoms) will be performed before and after the Calypso beacon implant. The information concerning the implant and the patient monitoring will be noted in the medical record. Patients will be instructed to contact the centre in case of any complication after the beacon implantation.

7.2.3. DURING RADIOTHERAPY

Toxicity evaluation will be done.
Toxicities will be assessed every week during radiation period according to the CTCAE V4.03.

7.2.4. END OF RADIOTHERAPY

- Clinical examination,
- Toxicity evaluation (CTCAE V4.03),
- Quality of life using QLQ-C30 and QLQ-PR25 questionnaires,
- IPPS and IIEF5 questionnaires.

7.2.5. FOLLOW-UP PERIOD (1, 3, 6, 12, 18, 24, 36, 48, 60 MONTHS FROM THE END OF RADIOTHERAPY)

- Clinical examination,
- Toxicity evaluation (CTCAE V4.03),
- PSA test,
- Quality of life using QLQ-C30 and QLQ-PR25 questionnaires,
- IPPS and IIEF5 questionnaires.

8. Assessment endpoints

8.1. PRIMARY ENDPOINT

The primary endpoint is defined by the incidence of grade ≥ 2 late pelvic toxicities between 3 months and 2 years after treatment (based on the Common Terminology Criteria for Adverse Events Version 4.03).

8.2. SECONDARY ENDPOINTS

The secondary endpoints include:

- Any acute toxicity (until 3 months post radiotherapy)
- Any late toxicity (between 3 months and 2 years post radiotherapy),
- Biochemical relapse-free survival (BRFS) at 5 years is assessed by PSA tests: PSA nadir + 2*,
- Complication relapse-free survival (CRFS) (at 2 years)* *,
- Complication relapse-free survival (CRFS) (at 5 years)* *,
- Quality of life evaluation using EORTC QLQ-C30 and QLQ-PR25 questionnaires before and at the end of treatment and at each evaluation (1 month, 3 months, every 6 months until two years then every year from end of radiotherapy),
- Specific questionnaires for urinary obstruction (IPSS) and for erectile function (IIEF5) before and at the end of treatment and at each evaluation (1 month, 3 months, every 6 months until two years then every year from end of radiotherapy),
- Correlation between late toxicity (between 3 months and 2 years post radiotherapy) and the radiation-induced T-lymphocyte apoptosis (RILA) rate (low (≤15) versus high (>15)).

BRFS is defined as the interval between the date of randomization and the date of detection of a biochemical failure (definition below), clinical relapse or death, whichever occurs first.
Biochemical failure after radiation therapy is defined an increase in the PSA value more than the nadir of the PSA + 2 ng/ml.

**CRFS is defined as the interval between the date of randomization and the date of rectal or urinary grade 2 or more late toxicity, biochemical relapse, clinical relapse or death, whichever occurs first

COVID-19 Heath crisis, and after reporting data during this period, didn't have an impact on the protocol medical care of patients included in this study and therefore didn't have an impact on the assessment endpoint defined initially.

9. Rila test

The RILA test results will be used for the stratified randomization and for the correlation between the late toxicity and the RILA rates (see appendix 7).

For the RILA test, one 10 ml Lithium Heparin (LiH) blood tube should be collected on Monday or on Tuesday at baseline and before randomization.
Tubes will be identified with the subject's study code, date and time of sampling, and identification number of the investigational site.

The tubes will be then sent to the Institut de Recherche en Cancérologie de Montpellier - INSERM:

Laura Bourillon- Equipe AP (Laura.Bourillon@icm.unicancer.fr)
INSERM - U1194- IRCM (EX U896)
Magasin sous-sol du Bât. Recherche F2
31 rue de la croix verte
34298 MONTPELLIER CEDEX 05
(phone: 04 67 61 24 34)

10. Statistical considerations

10.1. SAMPLE SIZE CALCULATION

The primary endpoint of this study is the incidence of late pelvic grade ≥ 2 toxicities.

Sample size calculation for the experimental arm (Calypso system) will be based on a single-stage Fleming design for phase II trials. Fleming design is formulated in terms of success rate.

In the context of this study, we define a success as a patient without grade ≥2 late pelvic toxicity occurring after 3 months and until 2 years after treatment (based on the Common Terminology Criteria for Adverse Events Version 4.03).

Considering that the common expected success rate in this indication is 85% (p0), the smallest success rate expected in the experimental arm is set at 95% (p1). Using a one-stage Fleming design with one-sided $\alpha=0.05$ and $\beta=0.10$, it will be necessary to include 75 evaluable patients.
Taking into account a 10% rate of non-evaluable patients, a total of 83 patients will be required in Calypso arm.

The number of success will be evaluated on the first 75 evaluable patients.

The experimental treatment (Calypso system) may be considered sufficiently safe if at least 69 patients (among 75 evaluable patients) show a treatment success, otherwise the Calypso system will be considered as insufficiently safe.

Stage	Nb. of patients	Insufficiently safe if	Sufficiently safe if
1	75 first evaluable patients	≤68 successes	≥69 successes

A concurrent control arm of a size equal to half that experimental, that is 38 patients, will be included in the study using a 2:1 randomization ratio (Calypso : Control).

Taking into account a 10% rate of non-evaluable patients, a total of 83 patients will be required in CALYPSO arm whereas 42 patients in Control arm.

Accordingly, **a total of 125 patients will be recruited in the trial**, 83 and 42 patients in Calypso and Control (IGRT) arms respectively.

The control group is used as a validation of the hypothesis that success rate without Calypso system is 85%. The 90% Confidence Interval (90%CI) of the success rate will be estimated on the 38 evaluable patients of the control group. If 85% is included in the 90%CI, the final conclusion will be the Fleming design conclusion. Conversely, if 85% is not included in the 90%CI, the final conclusion will be taken as follows:

IGRT (Control) Group : observed 90%CI	Calypso system : Fleming plan	
	Positive result	Negative result
85% < lower boundary	Discuss the result	Fleming design conclusion
85% within the 90%CI	Fleming design conclusion	Fleming design conclusion
85% > upper boundary	Fleming design conclusion	Discuss the result

Randomisation will be stratified according to the:

- RILA test (low (≤15) versus high (>15)),
- Indication for hormonotherapy (yes versus no),
- Anticoagulation treatment (yes versus no),
- Diabetes patient status (yes versus no)

Note: Sample size is not modified. The proposed change on prescribed dose and fractioning does not alter the original scope of the research as the result of the above cited large non-inferiority trials provide enough evidence of no difference in late pelvic toxicity between normofractionned and moderate hypofractionation. Nonetheless, a subgroup analysis is henceforth planned and a meta-analytic approach will be used to provide a pooled estimation of the proportion of success (and its IC95%) in the experimental Calypso arm (cf. §10.2. Statistical analysis).

10.2. STATISTICAL ANALYSIS

A detailed statistical analysis plan (SAP) will be elaborated before the database is frozen. No formal statistical comparison will be made between the treatment arms.

Data will be summarized using frequencies and percentages for categorical variables and using medians and ranges for continuous variables.

The percentage of patients without grade≥2 late pelvic toxicity (P_{obs}) (success) occurring after 3 months and until 2 years after treatment, as well as the percentage of patients experiencing at least a grade≥2 late pelvic toxicity in that period (1-P_{obs}; primary endpoint of the trial) will be presented for each arm with their respective 90% (and 95%) confidence interval based on binomial exact distribution.

The decision about the effect of the experimental arm (Calypso system with reduction of treatment margins) in terms of late pelvic toxicity rate will be stated according the decision rules described in previous section (sample size calculation).

Moreover, in order to control for the additional heterogeneity introduced with the switch to moderate hypofractionation RT we will use a meta-analytic approach in order to consider this factor (i.e. the fractionation-group: normofractionned or moderate hypofractionned) into the calculation of a global pooled proportion of success (and its IC95%) in the experimental Calypso arm.

This analysis will be performed using the Metaprop Stata module, implemented to perform meta-analysis of proportions in the Stata software (References are listed here below). A random effect model will be used to calculate a pooled global estimated of the proportion of success. Metaprop also allows computation of 95%CI using the score statistics and the exact binomial method, and incorporates the Freeman-Tukey double arcsine transformation of proportions. I^2 statistic will be used to describe the percentage of total variation due to the inter fractionation-group heterogeneity. All the details concerning this part of the analysis will be also specified in the SAP [44, 45].

Biochemical and complication relapse-free survival curves will be estimated using the Kaplan-Meier method.

The analysis of QLQ C30 and QLQ PR25 questionnaires will be performed in accordance with the EORTC guidelines.

Specific questionnaires for urinary obstruction (IPSS) and erectile function (IIEF5) will be described at each evaluation and over time.

Subgroup analysis: a subgroup analysis into the experimental arm (Calypso system) will be conducted between the subgroup of patients that have followed a conventional RT and those who have followed a hypofractionned RT. This analysis concerns mainly the primary endpoint as well as toxicity-related secondary endpoints.

All statistical analyses will be performed with the Stata v16 software (StataCorp LP, College Station, TX).

Note: previous to the present protocol modification, an analysis was conducted on December 2020, focussed on the incidence of pelvic late grade ≥ 2 toxicity. This analysis based on 35 evaluable patients in Calypso system (24 evaluable in RTGI standard) revealed only two failures overall, one in each group.
Despite of this interim analysis, the planned sample size in this phase 2 trial (non-comparative) still large enough for a final analysis with an adequate final trade-off between α and β errors.

Statistical reports planned:

According to estimated study duration (Paragraph § 2.2):

The final statistical analysis is planned at the end of 2028 (end of inclusions planned for April 2026) including primary and secondary endpoints with a minimal median follow-up of 5 years. A statistical report will be delivered at that occasion.

10.3. STUDY POPULATION

All statistical analyses will be performed on an intent-to-treat (ITT) basis and per-protocol (PP) population.

Populations for analysis are defined as follows:

Intent-to-treat (ITT) population includes all patients who were randomized to one treatment, whether or not any study treatment was administered. Patients will be analyzed in the treatment group in which they were assigned by randomization.

PP population includes all eligible and evaluable patients.

The "Safety" Population includes all patients who received at least one administration of the treatment (radiotherapy).

10.4. MODIFICATIONS OF THE STATISTICAL ANALYSIS PLAN AND INITIAL STRATEGY

Any modification to the initial statistical analysis plan (SAP) will be detailed with all the necessary arguments reported in an updated version of SAP. These modifications can include supplementary or exploratory analyses that were not initially planned.

11. Procedures for data collection

Study data will be recorded on the case report form (CRF) by the person designated by the investigator. A CRF is required and should be completed for each included subject. It is the investigator's responsibility to ensure the integrity of the information transcribed in the CRF. CRFs must be signed by the investigator or by an authorized staff member. These signatures will attest that the information contained in the CRFs is true. The investigator agrees to keep records, including the identity of all participating subjects, all original signed informed consent forms, copies of all CRFs, and source documents.

It is the expectation of the Sponsor that all data entered into the CRF has source

documentation available at the investigational site. The Study Data Management Center (Biometrics unit of Montpellier Cancer Institute) will record source documentation into a database in an ongoing basis. Systems with procedures that assure the quality of every aspect of study data management will be implemented, using Clinsight® software v6.2.

12. Vigilance

According to Article R1123-46 of the Public Health Code, Regulation (EU) 2017/745 of the European Parliament and of the Council of April 5, 2017 on medical devices (MDCG) and the MDCG 2020-10 / 1

12.1. ADVERSE EVENTS ((MDR Article 2 (57))

12.1.1. DEFINITION

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

An Adverse Event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered an investigational radiotherapy/product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (for example: an abnormal laboratory finding), symptom, disease, or worsening of a pre-existing medical condition temporally associated with the use of an investigational radiotherapy/product, whether or not considered related to the investigational radiotherapy/ product.

Disease progression in not an AE.

Only abnormal laboratory findings that are clinically significant should be considered an AE. Abnormal laboratory findings are clinically significant if an active medical intervention is indicated, such as a dose modification of the investigational radiotherapy/ product; an interruption of the investigational radiotherapy/ product; the withdrawal of the investigational radiotherapy/ product; the introduction of a (symptomatic) treatment; the performance of additional diagnostic procedures; the increase in monitoring frequency.

An AE related to the investigational radiotherapy/ product is also called an adverse reaction or effect. Disease progression is not an AE.

12.1.2. COLLECTION AND REPORTING OF ADVERSE EVENTS

Every AE occurring during the clinical trial should be recorded on the corresponding page of the Case Report Form. Every AE should be documented, monitored and followed until the AE is recovered or until 5 years after the end of the radiation period.

Clinically significant abnormal laboratory findings should be monitored regularly by specific analysis until their values return within the normal reference ranges, to the baseline value or until an adequate explication of the out of range value has been found.

For every AE, the following items will be documented by the Investigator:

- A clear description of the event using the adequate medical terms;
- The seriousness of the event;
- The severity or grade of the event (severity criteria are described in the next paragraph);
- The onset and end dates of the event;
- The actions taken and the necessity to introduce a corrective treatment or not;
- Whether the AE caused or not the withdrawal of the subject from the study;
- The outcome of the event. In case of a non-fatal outcome, the AE should be documented until recovered, until the return to baseline conditions of the event or until stabilization of the event's sequelae (the nature of the sequelae should be documented) ;
- The causality between the event and the device/investigational radiotherapy/ product;
- The eventual causality between the event and the study procedures (time laps without treatment, complementary assessments required by the protocol, etc.), the study pathology, a concomitant treatment, a concomitant pathology or any other factor.

12.1.3. SEVERITY CRITERIA

The severity criteria should not be mistaken with the seriousness criteria which determine the conditions of notification. The severity or grade of adverse events is evaluated by the Investigator following the NCI-CTCAE classification version 4.03.

The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (Activities of Daily Living)*.
- Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 = Life-threatening consequences; urgent intervention indicated.
- Grade 5 = Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

12.2. DEVICE EFFECT

An adverse device effect is an adverse event related to the use of an investigational device. A serious adverse device effect is an adverse device effect that has resulted in any of the consequence characteristics of a serious adverse event

12.3. DEVICE DEFICIENCY (MDR Article 2(59))

Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied

by the manufacturer.

12.4 SERIOUS ADVERSE EVENTS (MDR Article 2(58))

12.4.1 DEFINITION

A Serious Adverse Event (SAE) is an adverse event which:

- results in death
- serious deterioration in the health of the subject, that resulted in any of the following:
  - is life-threatening illness or injury
  - permanent impairment of a body structure or a body function,
  - requires in-patient hospitalization or prolongation of existing hospitalization,
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
  - chronic disease,
- foetal distress, foetal death or a congenital physical or mental impairment or birth defect

12.4.2 Reportable events

The following events are considered reportable events in accordance with MDR Art. 80(2)

a- any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;

b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

c) any new findings in relation to any event referred to in points a) and b)

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to a reaction that hypothetically might have caused death if more severe.

A hospitalization scheduled by the protocol (biopsy, hormonotherapy...) is not considered a SAE. A hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE is not considered a SAE. A hospitalization planned prior to patient enrolment is not considered a SAE, provided that his occurrence/outcome is clearly not aggravated by investigational device/radiotherapy/ product.

Disease progression or any medical event related to disease progression linked to disease under study is not considered a SAE.

The terms "disability" and "incapacity" match with all physical/psychological temporary or permanent handicaps, clinically significant with consequences for physical or mental functioning and/or the patient's quality of life of the patient.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious events, such as important medical events that might not be

immediately life-threatening or result in death or hospitalization but might put at risk the subject or might require intervention to prevent one of the other outcomes listed above. Such events are considered serious with seriousness criterion "medically relevant". Examples of such events are allergic bronchospasm, torsade de pointes or convulsions.

The EudraVigilance Expert Working Group (EV-EWG) has coordinated the development of an Important Medical Event Terms (IME) list, which could help Investigators to determine whether an AE is serious or not:

http://eudravigilance.ema.europa.eu/human/textforIME.asp

The IME list is intended for guidance purposes only, and is not a mandatory requirement for seriousness assessment and regulatory reporting.

Another example of a serious adverse event with seriousness criterion "medically relevant" is a suspected transmission via a medicinal product of an infectious agent.

12.5 CAUSALITY

For every SAE the Investigator and the Sponsor evaluate separately the possible causal relationship to the investigational device/ radiotherapy/ product. These evaluations might be different one from the other (for example: in the Investigator's opinion the SAE is not related to the investigational device/radiotherapy/ product and in the Sponsor's opinion the SAE is related to the investigational device/ radiotherapy/ product).

The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse even shall be assessed and categorized.

During causality assessment activity, clinical judgement shall be used and the relevant documents, shall be consulted. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

For the purpose of harmonizing reports, each SAE will be classified according to four different levels of causality:

1. Not related
2. Possible
3. Probable
4. Causal relationship

The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational device, the comparator or the investigation procedure.

12.5.1 UNANTICIPATED SADE (**MDCG 2020-10/1 10.2.18- RDM (EU) 2017/745**

An Unanticipated Serious Adverse Device Effect is an effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. Procedures associated with the use of a device should be addressed in the risk assessment, which makes it possible to determine whether the procedure related SAEs are Unanticipated Serious Adverse Device Effect or not. SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device should not be considered Serious Adverse Device Effects.

The Sponsor evaluates the unexpectedness of the SAE by consulting the study protocol and instruction for use of beacon care package for prostate.

12.5.2 NEW EVENT (article R1123-46 du CSP) :

Any new data leading to a reassessment of the benefits / risks balance of the research or product of the research, to changes in the use of the product or in the conduct on documents related to the research, or to discontinuation, arrest or modification of the research protocol or that of similar research.

12.5.3 SAE/New Event, DEVICE DEFICIENCY, NOTIFICATION PROCEDURE

Every SAE, expected or unexpected, any device deficiency leading to SAE occurring during the study period (from the signature of the informed consent form until up to 2 years after the end of the radiation period) should be notified to the Sponsor without any further delay, using the "Serious Adverse Event Notification Form" (Appendix 8). This form should be completed following the completion instructions (Appendix 9) and be send to the ICM Clinical Research Pharmacovigilance Unit:

E-mail: Notification-EIG-DRCI@icm.unicancer.fr

Every SAE occurring beyond the 2 year-period after the withdrawal of the investigational radiotherapy/, judged by the investigator to be related to the device or device deficiency leading to SAE / investigational radiotherapy, or to the research should also be notified to the sponsor in the same conditions as every other SAE.

The "Serious Adverse Event Notification Form" should be completed in English and only one diagnosis or one symptom (except for linked symptoms) should be reported to enable the MedDRA coding. If several symptoms are documented in the source documents, only the main symptom will be reported as verbatim on the notification form.

After the initial notification, a follow-up report should be completed and sent every time complementary information on the SAE becomes available. Finally, when the case is closed, a final report with the complete information should be completed and sent to the Pharmacovigilance Unit (Notification-EIG-DRCI@icm.unicancer.fr)

Complementary information or clarification may be requested by the Sponsor using Data Clarification Forms (DCFs). The Sponsor could also ask the site to send the anonymized medical records or laboratory findings corresponding to the SAE. The ICM, as the Sponsor of the trial, receives all SAE Notification Forms and evaluates the imputability and the expectedness of the SAEs.

For other safety information:

E-mail: Pharmacovigilance-icm105@icm.unicancer.fr

Mme Nadia BENSMAIL
Clinical Research Pharmacovigilance Unit
Institut régional du Cancer Montpellier, Bât. A
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Fax: +33 4 67 61 31 04

The risk-benefit balance of the study is evaluated continuously by the ICM Clinical Research Pharmacovigilance Unit and this risk-benefit balance will be discussed in the periodic safety reports. These reports will contain all required regulatory aspects and will be submitted to the competent authorities.

13. Quality assurance

13.1. MANAGEMENT OF THE STUDY

In order to guarantee the authenticity and the credibility of the data according to GCPs, the Sponsor sets up a system of quality assurance, this comprises:
- Management of the study according to the procedures of the Clinical Research Unit,
- Quality control of data of the investigational site by the monitor whose role is to verify the similarity and coherence of CRF data compared to the source documents. Monitors will contact investigational sites prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibility to satisfy ethical and regulatory requirements.

The investigator should maintain a list of appropriately qualified persons to whom he/she as delegated trial duties. Study staff involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

13.2. CONFIDENTIALITY

The coordinators commit themselves all the persons necessary for the performance of the trial, to guarantee the confidentiality of all information related to the project until the publication of the study results. The obligation of confidentiality will not be applied to the information that the investigator has to communicate to the patients in the context of their participation in the trial or to information already published. The investigator commits himself not to publish, disclose or use, in any way, directly or indirectly, the scientific or technical information related to the study.

13.3. ARCHIVING

Regarding patient clinical source documents, subject notes must be kept for the maximum time period permitted by the hospital, institution or private practice. Essential documents (copies of patients CRF and the Investigator's Trial File) will be securely archived by the Sponsor for 15 year duration in accordance with the applicable regulatory requirement of the European Good Clinical Practices. Subject files may be reviewed under the investigator's responsibility, and will be readily available upon authorities' request.

14. Ethical and Regulatory considerations

The study will be conducted in accordance with the protocol, Good Clinical Practices (GCPs) guidelines as defined by the International Conference on Harmonization (ICH), the French regulations in force, namely the French Public Health Law No 2004-806 of 9 August 2004

(Loi no 2004- 806 du 9 août 2004 relative à la politique de santé publique), the Bioethical Laws, the ethical principles that have their origin in the Declaration of Helsinki (appendix 14) and the the Informatics and Freedom Law and the European Regulation 2016/679 concerning the protection of the physical persons towards the personal data processing and concerning the free circulation of these data says "RGPD" (Règlement Général sur la Protection des Données)
This study is registered at the ClinicalTrials.gov website (http://clinicaltrials.gov/): Identifier NCT03254420

14.1. ETHICS COMMITTEE

This study has received the approval from the local Ethics Committee (CPP Sud Méditerranée III, Ref.2015.12.05).

14.2. SUBJECT INFORMATION AND CONSENT

The patient's written informed consent must be obtained by the investigator or a person designated by the investigator before collecting any personal data. The written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. The patient will be encouraged to ask the study investigator or delegate any question concerning the study and to discuss the study with any individual or other medical personnel. In addition, the patient will be offered the option to take home the consent forms and review them at her/his convenience and to discuss the study with other individuals to determine whether to participate in the study.

15. Study insurance

As study Sponsor, the Montpellier Cancer Institute (ICM) has subscribed to an insurance against civil liability in accordance with the applicable regulatory requirements of the Article L1121-10 of the French Public Health Code: SHAM – 18 rue Edouard Rochet - 69372 Lyon Cedex 08 (contract n° 140.474).

16. Publication Policy

The authors of the publications will be the persons who i) draft the article or revise it critically for intellectual content, ii) substantially contribute to conception, design, data collection, analysis and interpretation of data, iii) approve the final version to be published. No information can be used for publication or oral presentation without the written agreement of the study coordinator.

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