PROGERAD Protocol

Registration No.: No 2014-A00300-47

Ref: ICO-A-2014-04

CPP Ref.: 2014/05

“Cancer of the PROstate in patients over 75 years: Geriatric Determinants of the overall impact

raditherapy with curative aim"

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SIGNATURE PAGE

SIGNATURE OF THE RESEARCH MANAGER

The principal investigator commits to conducting this study in routine care in accordance with all legislative and regulatory provisions that may apply to the research and according to the protocol.		
Name and position of the representative signatory: Pr François-Régis BATAILLE Chief Executive Officer	Date:	Signature:

INVESTIGATOR SIGNATURE

I have read all pages of the clinical trial protocol for which the ICO is the responsible research; I confirm that it contains all information necessary for conducting the trial. I commit to carry out the trial in accordance with the protocol and the terms and conditions defined therein.

I am aware that this research falls within the framework of routine care research as defined by paragraph 2 of Article L 1121-1 and Article R 1121-3 of the French Public Health Code. The procedures are performed and products used in the usual manner, but specific monitoring modalities are provided through this protocol.

I commit to conducting the trial in compliance with:

- the principles of the Helsinki Declaration,
- the rules and recommendations of international good clinical practice (ICH-E6) and French good clinical practice rules for biomedical research involving human-use medicines - decisions of November 24, 2006)
- national legislation and regulations relating to clinical trials
- compliance with the EU Clinical Trials Directive [2001/20/CE]

I also commit that investigators and other qualified members of my team have access to copies of this protocol and documents related to the conduct of the trial to enable them to work in compliance with the provisions set out in these documents.

	Name:	Date:	Signature:
Investigators coordinators	Dr Stéphane SUPIOT Dr Aurore GOINEAU		

LIST OF ABBREVIATIONS

ANSM	National Agency for Medicines and Health Product Safety
ARC	Clinical Research Associate
GCP - Good Clinical Practice	Good Clinical Practices
IRB - Institutional Review	People Protection Committee
CNIL	National Commission on Information Technology and Civil Liberties
CCTIRS	Consultative Committee on Information Processing in Matters Research in the Health Field
e-CRF	electronic-Case Report Form (observation log)
Clinical Research Delegation	Delegation for Clinical Research and Innovation
European Organisation for Research and	European Organisation for Research and Treatment of Cancer
Institute of Oncology of the West	Institute of Oncology of the West
Body Mass Index	Body Mass Index
IMRT	Intensity-Modulated Radiation Therapy
National Cancer Institute	National Cancer Institute
Performance Status	Performance Status
Multidisciplinary Team Meeting	Multidisciplinary Team Meeting

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1. JUSTIFICATION OF THE STUDY

With more than 60,000 new cases per year in France, prostate cancer is the most common cancer in men. It mainly affects older individuals. For patients over 70 with localized prostate cancer, radiotherapy is most often offered, whether alone or combined with hormone therapy. Although long-term severe morbidity from the treatment remains low and infrequent, irradiation leads to frequent short-term morbidity, sometimes disabling in the elderly. In a multidisciplinary tumor board, the question of the indication for radiotherapy with curative aim in the elderly over 75 with locally advanced prostate cancer is often raised. Reluctance to this curative treatment is mainly related to the risks of acute urinary and digestive toxicity and to the asthenia that this toxicity can cause, reinforced by the 30 to 40 daily treatment visits. Thus, faced with elderly and/or frail patients, selecting those who will benefit from this treatment can be difficult for the physician. Despite the rise of gero-oncology and the recently developed screening tools (type G8), resources remain limited and unevenly distributed. It would therefore be particularly interesting for the practitioner to have markers that allow predicting poor tolerance of curative radiotherapy for prostate cancers.

Since 2006, we have prospectively evaluated the quality of life of a cohort of patients with localized prostate cancer treated with curative-dose radiotherapy using techniques considered to produce the least toxicity, such as intensity-modulated conformal radiotherapy (IMRT) (1-2). In these patients with a median age of 73, we showed that irradiation caused a transient deterioration of quality of life at the end of radiotherapy. The overall quality of life deterioration was moderate in 31.5% of patients and significant in 10.5% of patients and was significantly worsening when hormone therapy, prior transurethral resection of the prostate, or cardiovascular disease was used. It is therefore important to carefully select patients at risk of quality-of-life deterioration to offer this potentially deleterious treatment only to patients able to tolerate it.

Currently, very few elderly patients with localized prostate cancer are evaluated by an oncogeriatrist before starting curative radiotherapy. Oncogeriatric clinical research in prostate cancer has so far focused mainly on diagnosis and tolerance of chemotherapy (3–5) or hormone therapy (6–9). Paradoxically, while radiotherapy is the most commonly offered treatment to elderly patients, studies in oncogeriatrics specifically aimed at radiotherapy for prostate cancer in elderly subjects are rare and most often retrospective (10–13).

We propose to conduct a prospective analysis of the physical, psychological, cognitive, and social impact of radiotherapy on any patient aged 75 and older with localized prostate cancer indicated for curative radiotherapy. A standardized geriatric assessment will collect information on social, functional, sensory, cognitive, emotional, motor, nutritional, and medical factors concerning comorbidities. This assessment will be performed before radiotherapy and at 6 months. The patients’ quality of life will be

evaluated by the QLQ-C30 questionnaire of the EORTC before starting treatment, then 2 and 6 months after the end of radiotherapy. This short follow-up interval seems relevant in this elderly population and will allow obtaining a response within 2.5 years to the issue raised in clinical practice (24 months of inclusion and 6 months of follow-up).

ICO Nantes treats by radiotherapy about 45 patients over 75 years old with localized prostate cancer per year. Over 24 months of inclusion, considering 5 centers with geriatric assessment (ICO Nantes, Angers, CHD de La Roche-sur-Yon, Centre Catherine de Sienne de Nantes and Centre Etienne Dolet de Saint Nazaire, CHU Henri Mondor Créteil), we hope to reach 230 patients to have 200 evaluable patients in 24 months.

Overall, this is a prospective, multicenter study, reflecting daily clinical practice questions for a pathology that represents a major public health issue. This study will use internationally validated tools (standardized geriatric assessment and the EORTC QLQ-C30 questionnaire). Its implementation is simple, with excellent patient acceptability (questionnaires), presumably allowing easy adherence by radiotherapy centers and inclusion of a large number of patients. This study will provide original and important information for clinical decisions in a field where oncology-geriatric studies are still relatively few.

The sexual function will be evaluated by the simplified IIEF questionnaire before radiotherapy, then at 2 and 6 months.

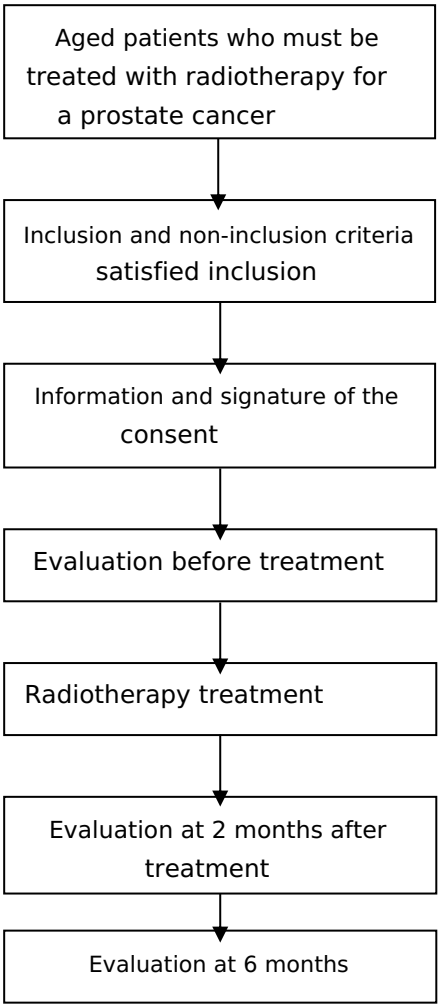
The biochemical relapse delay will be evaluated by PSA dosage before radiotherapy, then at 2 and 6 months.

3. RESEARCH DESIGN

3.1. GENERAL METHODOLOGY OF THE RESEARCH

This research is an interventional study of standard care, prospective, multicenter, non-randomized.

3.2. STUDY SCHEME



2. OBJECTIVES AND EVALUATION CRITERIA

2.1. PRIMARY EVALUATION OBJECTIVE AND CRITERION

2.1.1. Primary objective

To determine, in elderly patients treated with radiotherapy for prostate cancer, a predictive score of general impact (physical, psychological, cognitive, and social status) integrating geriatric criteria.

2.1.2. Primary evaluation criterion

The primary evaluation criterion will be the overall tolerance of radiotherapy, assessed using the EORTC QLQ C30 questionnaire. Tolerance will be considered poor in the event of a loss of 20 points or more (out of 100) between the baseline assessment and the assessments at 2 and 6 months. Tolerance will be considered acceptable in other cases. This 20-point threshold was chosen according to the work of Osoba (14).

Different parameters that may affect this overall tolerance will be studied: ADL, IADL, MMSE, mini GDS, MNA, CIRS-G, BMI scores, time obtained on the « timed get up and go » test, distance between home and the radiotherapy center, number of concomitant treatments, and supportive care implemented.

2.2. SECONDARY OBJECTIVES AND EVALUATION CRITERIA

2.2.1. Secondary objective(s)

We will assess:

- - urinary function at 2 and 6 months compared with baseline,
- sexual function at 2 and 6 months compared with baseline,
  the time to biochemical relapse.

2.2.2. Secondary evaluation criterion(s)

Urinary function will be assessed using the IPSS questionnaire before radiotherapy, and then at 2 and 6 months.

4. POPULATION STUDIED

4.1. DESCRIPTION OF THE POPULATION

The target population corresponds to men over 75 years of age, carriers of a prostate adenocarcinoma, with an indication for radiotherapy with curative intent. A hormonal therapy treatment may be ongoing or started following radiotherapy.

4.2. INCLUSION CRITERIA

1) Man with histologically proven prostate cancer
2) Indication for radiotherapy with curative intent
3) Age ≥ 75 years
4) Patient having signed informed consent

4.3. NON-INCLUSION CRITERIA

1) Patient managed for metastatic prostate cancer
2) Patient unable to undergo protocol follow-up for social, geographic, or family reasons

3) Person not affiliated with a social security system or beneficiary of such a system

4) Adults under guardianship

5. PROGRESS OF THE STUDY

5.1. SELECTION OF PATIENTS

During the information consultation with the radiotherapist, the study will be offered to patients meeting the inclusion and exclusion criteria.

5.2. PRE-TREATMENT EVALUATION

This evaluation must take place before the start of radiotherapy and includes:

- the recovery of the informed consent dated and signed by the patient,
- a clinical examination including weight (BMI calculation),
- - the quality of life assessment by the QLQ-C30,
  the assessment of urinary and sexual function with IPSS and IIEF
- a PSA measurement within less than 2 months
- an oncogeriatric consultation with assessment:
  ADL
  IADL
  MMSE
  Mini-GDS
  MNA
  CIRS-G
  timed get up and go test?,
  recovery of concomitant treatments usage.

5.3. EVALUATION AT 2 MONTHS

This evaluation must take place 2 months after the end of radiotherapy and includes:

- a clinical examination including PS and weight (BMI calculation),
- - the quality of life assessment by the QLQ-C30,
  the assessment of urinary and sexual function with IPSS and IIEF,
- a PSA measurement within less than 1 month.

5.4. FOLLOW-UP AT 6 MONTHS

This evaluation must take place 6 months after the end of radiotherapy and includes:

- a clinical examination including PS and weight (BMI calculation),

- the assessment of quality of life using the QLQ-C30,
- the assessment of urinary and sexual function with IPSS and IIEF,
- a PSA test from less than 2 months ago,
- an onco-geriatric consultation with assessment of:
    - ADL
    - IADL
    - MMSE
    - Mini-GDS
    - MNA
    - CIRS-G
    - timed get up and go test ,
    - recovery/recording of the use of concomitant treatments.

5.5. TREATMENT

Radiotherapy treatment will be decided according to national recommendations validated by the INCa and according to the choice of the referring physician in agreement with the RCP, and remains completely independent of the research. Treatment modalities are at the discretion (conformal radiotherapy or IMRT, curative dose, prostate in place or post-operative).

In accordance with usual practice, hormone therapy may be given concurrently with radiotherapy or started after the end of radiotherapy treatment. Patients who may or may not have undergone surgery.

All supportive care deemed useful for the patient by the investigator may be offered to the patient (physiotherapy session, psychological support, consultation with a dietitian, physical activity session, session with a socio-aesthetician ...).

5.6. STUDY TIMELINE

	Assessment before radiotherapy	Assessment at 2 months	Assessment at 6 months
Collection of informed consent	x (or before)		
Clinical examination	x	x	x
Quality of Life Assessment (QLQ-C30)	x	x	x
Onco-geriatric assessment (ADL, IADL, MMSE, Mini-GDS, MNA, CIRS-G, timed get up and go test, concomitant therapies)	x		x
Evaluation of urinary and sexual functions (IPSS and IIEF)	x	x	x
PSA measurement	In both month	Within the month	In both month

5.7. IDENTIFICATION OF ALL SOURCE DATA NOT LISTED NOT IN THE MEDICAL RECORD

Quality of life questionnaires and onco-geriatric tests will not be in the patient's source data. They will be made available in a per-patient folder in the investigator binder to be transcribed into the e-CRFs.

Other patient data related to monitoring outside the trial will be collected in their medical record.

5.8. TERMINATION RULES OF PARTICIPATION OF A PERSON

5.8.1. Criteria for premature cessation of participation of a person in research

Patients may withdraw their consent and request to exit the trial at any time and for any reason, without losing the right to be treated by their physician. The investigator may also prematurely interrupt a patient's participation in the trial for any reason that would best serve the patient's interests, including the occurrence of an intercurrent illness or an adverse event. In the event of premature withdrawal, at any time and for any reason, the investigator must inform the patients if necessary and document the reasons as completely as possible.

Trial withdrawals shall be reported, notably for the following possible reasons:

- Death
- Withdrawal of consent
- Investigator's choice
- Lost to follow-up

5.8.2. Premature termination procedures of participation of a person in research

The modalities of medical management and follow-up in case of premature study termination for a given patient will be identical to usual practice outside the protocol.

5.8.3. Criteria for stopping the research (except considerations) biostatistics)

The end of the study will be defined as the last follow-up visit (at 6 months) of the last patient included.

Furthermore, the study may be interrupted for administrative reasons, and/or at the sponsor's decision. If the study is stopped prematurely or suspended, the person responsible for the study will immediately inform the CPP (Comité de Protection des Personnes) of the reason for the halt or suspension. In all cases, included patients will be followed as part of the study until the 6-month follow-up visit by the investigator.

6. DATA MANAGEMENT AND STATISTICS

6.1. DATA COLLECTION AND PROCESSING OF STUDY DATA

6.1.1. Data collection

An electronic Case Report Form (e-CRF) (CS Online Clinsight®, Cenon, France) will be created per patient. All information required by the protocol must be collected in the e-CRF. It must include the data necessary to confirm adherence to the protocol and all data necessary for statistical analyses, and to detect major deviations from the protocol.

The person(s) responsible for completing the e-CRF (investigator, CRC…) must be defined and identified in the responsibility delegation table kept in the investigator’s binder.

6.1.2. Data coding

By signing this protocol, the principal investigator and all co-investigators commit to keeping confidential the identities of patients who participated in the study.

The information required by the protocol will be kept confidential without mentions of first and last names in the e-CRF with a center identification number and a patient number. Only the first letters of the patient’s surname and given name will appear.

This code will be the only information appearing on the observation notebook (e-CRF) and will allow linking the e-CRF to the patient retroactively.

6.1.3. Data handling

For each patient, the set of data will be collected in the e-CRF. It will be completed by the investigator and/or the CRA that the investigator has designated for this task.

6.2. STATISTICS

6.2.1. Description of the planned statistical methods, including including the schedule of planned interim analyses

Descriptive analysis of the overall population:

Quantitative variables are described by their mean H the standard deviation as well as by their median and range. Qualitative variables are described by the frequency of their modalities.

Predictive analysis:

The aim here is to calculate a predictive score on part of the population (training sample - 2/3 of the patients) and then validate it on the remaining third that was not used to calculate the score.

- Determination of the predictive score

The training sample will be drawn at random among the 200 included patients. To allow subsequent extrapolation, this sample (2/3) will be compared with the test sample (1/3) to verify their comparability across all analyzed variables.

In the first univariate phase, the two groups of the training sample (overall poor tolerance or not) will be compared using the Student t-test (or Mann-Whitney if needed) for continuous quantitative variables and by Pearson's Chi-squared test (or Fisher's) for qualitative variables. The ROC curve will be drawn and the optimal discriminant threshold will be determined for each quantitative variable.

In the second multivariate phase, the optimal discriminant or logistic equation will also be calculated on the training sample. Multivariate analysis will be performed using logistic regression to obtain a multiple fit of the predictive model and to determine the statistically significant and independent predictive variables. This predictive equation will provide for each patient, based on their clinical characteristics and/or geriatric scores, a probability of belonging to the group 'significant deterioration'.

- Validation of the predictive score

Each patient in the test sample (who did not serve to determine the equation) will therefore be assigned to their theoretical progression group based on their theoretical percentage of risk of deterioration, determined by the previous equation of the predictive model (if p ≥ 50% => “deterioration” group, if p < 50% => “absence of deterioration” group). Then the concordance between the “theoretical” group x the “observed” group will be analyzed and the error rate calculated.

No interim analysis is planned; the analysis will be performed once the required number of evaluable subjects has been reached.

The software used will be SAS Software 9.3 (SAS Institute Inc. Cary, NC, USA). All tests will be two-sided, with a significance level p set at 5%.

6.2.2. Statistical justification for the number of enrollments

ICO Nantes treats with radiotherapy approximately 45 patients over 75 years old with localized prostate cancer per year. Over 18 months of enrollment, considering 5 centers with geriatric assessment (ICO Nantes, Angers, CHD de La Roche-sur-Yon, Centre Catherine de Sienne de Nantes and Centre Etienne Dolet de Saint Nazaire), we hope to reach 230 patients in order to have 200 evaluable patients within 18 months.

7. SAFETY

7.1. FOLLOW-UP COMMITTEE

The trial steering committee (comprising the coordinating investigator as well as a representative of the DRCI) will regularly verify the progress of the research in compliance with the protocol.

7.2. INDEPENDENT MONITORING COMMITTEE

For this study, it is not planned to appoint an independent monitoring committee.

7.3. ADVERSE EVENT

The occurrence of an Adverse Event related to the patient's management during this protocol will result in a report in the appropriate vigilance system (pharmacovigilance, biovigilance, hemovigilance, device vigilance, etc…).

8. ADMINISTRATIVE AND REGULATORY ASPECTS

8.1. RIGHT OF ACCESS TO DATA AND SOURCE DOCUMENTS

The medical data of each patient will be transmitted only to the supporting organization of the person responsible for the research or to any person duly authorized by it, under conditions that ensure their confidentiality.

If applicable, the supporting organization of the person responsible may request direct access to the medical record to verify the procedures and/or research data, without breaching confidentiality and within the limits permitted by laws and regulations.

8.2. COMPUTERIZED DATA AND SUBMISSION TO THE CNIL

The data collected during the study will be stored in a computer file complying with the "Data Protection and Liberties" law of January 6, 1978, as amended in 2004. This research has been subject to a request for an opinion to the CCTIRS and authorization by the CNIL.

8.3. TRIAL MONITORING

Monitoring will be ensured by the DRCI. A Clinical Research Associate (CRA) will verify:

1) The existence of the enrolled patients

2) The collection of signed informed consents and their archiving

3) Compliance with eligibility criteria (inclusion and non-inclusion)

4) The presence of the primary endpoint criterion

The monitoring plan is defined in consultation between the research team and the responsible institution, depending on the study objectives.

8.4. ETHICAL CONSIDERATIONS

8.4.1. Patient information

The investigator agrees to inform the patient clearly and fairly about the protocol (information note in appendix 1). He will give the patient a copy of the information note. This will specify the possibility for the patient to refuse to participate in the research.

8.4.2. Right of access to data and source documents

The medical data of each patient will be transmitted only to the sponsor or any duly authorized person by the sponsor, and, where applicable, to authorized health authorities, under conditions guaranteeing their confidentiality.

The sponsor and supervisory authorities may request direct access to the medical file for verification of procedures and/or trial data, without violating confidentiality and within the limits allowed by laws and regulations.

Data collected during the trial may be subject to computer processing, in compliance with CNIL requirements.

8.4.3. People Protection Committee

The study leader commits to submitting the study project for prior authorization by a People Protection Committee (CPP). The information provided relates, on the one hand, to the modalities and nature of the research and, on the other hand, to the guarantees provided for patients participating in this trial.

The CPP West II of Angers gave a favorable opinion on the implementation of this research on 11/04/2014.

The research was declared to ANSM which gave the RCB number: 2014-A00300-47.

8.5. AMENDMENTS TO THE PROTOCOL

Requests for substantial modifications will be sent by the study leader for review to the relevant ethics committee.

The modified protocol will be subject to an updated dated version. The information note will be modified if necessary.

8.6. RULES RELATING TO PUBLICATION

All information resulting from this trial is considered confidential, at least until the appropriate analysis and the trial monitoring by the sponsor, the coordinating investigator, and the trial statistician have been completed.

All publications, abstracts or presentations including the trial results must be submitted for approval to the sponsor (ICO).

In addition, all communications, manuscripts or presentations must include an entry that must state the ICO, all institutions, the investigators, the cooperating groups, the learned societies that have contributed to carrying out the trial, as well as the organizations that financially supported the research.

The authors will be defined according to the number of cases recruited by participant in the research and include :

- the study coordinator (first author or last author) ;
- the investigators who recruited the most patients (cited according to their rank of recruitment);
- the study statistician in 3rd position.

In the event of a dispute, the order of the authors will be decided by the sponsor (ICO).

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List of annexes

- ANNEX 1 Information letter and patient consent form
- ANNEX 2 Quality of Life Questionnaire QLQ-C30
- ANNEX 3 IPSS Questionnaire
- ANNEX 4 Simplified IIEF Questionnaire
- ANNEX 4 Onco-geriatric assessment tests
- ANNEX 5 Opinion of the Ethics Committee