PROTOCOL OLIGOPELVIS 1_GETUG P07

A) CLINICAL TRIAL IDENTIFICATION	
STUDY TITLE	Multicentric phase II study of high-dose radiotherapy and hormone therapy in oligometastatic relapses of the pelvic lymph nodes of prostate cancer
SHORT TITLE	OLIGOPELVIS 1_GETUGP 07
INVESTIGATOR COORDINATOR	Pr Stéphane SUPIOT
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B) STUDY BACKGROUND

There is a growing body of evidence reporting the existence of a subset of prostate cancer patients who, at relapse, present with a limited number of metastases (fewer than five lesions). This oligometastatic state has also been identified in other tumor types, such as melanoma, soft tissue sarcoma, liver, lung, and breast cancers, and has led to a shift in management toward more aggressive local treatments, including surgical resection.

Positron Emission Tomography–Computed Tomography (PET-CT), using tracers such as choline or acetate, has proven to be a reliable tool for detecting oligometastatic disease following biochemical recurrence in prostate cancer. For patients in this setting, an intensified therapeutic approach—combining androgen deprivation therapy (ADT) with high-dose radiation therapy directed at PET-CT-detected lesions—may be proposed.

This strategy has the potential to prolong the interval between successive courses of ADT or, in selected patients with a limited metastatic burden, may even offer the possibility of cure.

In this study, the investigators aim to evaluate the 2-year biochemical or clinical relapse-free survival of prostate cancer patients with 1 to 5 oligometastases treated concomitantly with high-dose conformal radiation therapy and LH-RH agonists.

C) STUDY INFORMATION

INDICATION	Oligometastatic lymph nodes pelvic prostate cancer patients
METHODOLOGY	Non randomized, prospective, national multicentre, phase II

Primary Objective and Endpoint

Primary objective	Endpoint	Evaluation time
The primary objective is to evaluate the biochemical or clinical relapse-free survival at 2 years.	The primary endpoint is the 2-year relapse-free survival probability. Biochemical or clinical relapse is defined as: • A PSA level higher than the pre-treatment PSA value, confirmed by	2 years

	two consecutive increases measured in the same laboratory; and/or • An increase in the number of metastatic sites on follow-up imaging assessments.	
SECONDARY OBJECTIVES AND ENDPOINTS		
Secondary objectives	**Endpoints**	**Evaluation time**
a) Biochemical relapse-free survival	A PSA > 0.2 ng/mL after the post-treatment nadir (or PSA > nadir + 0.2 ng/mL if nadir > 0.2 ng/mL). For patients without a history of prostatectomy, biochemical recurrence is defined by: • A PSA > pre-treatment nadir **AND** • A PSA > 0.2 ng/mL after the post-treatment nadir	2 years
b) Time to resumption of hormone therapy	Resumption of hormone therapy	5 years
c) Time to initiation of any subsequent treatment	Resumption of any treatment	5 years
d) Assessment of toxicity (acute toxicity assessed 1 month after the end of radiotherapy, and late toxicity assessed at 2 years), with particular attention to gastrointestinal events	NCI-CTC-AE v4.0 scale	5 years
e) Site of relapse: within the irradiated field or at distant (non-irradiated) sites	At least one morphological imaging (depending on recurrence location and center practice): • Abdominopelvic CT scan • and/or Pelvic MRI • and/or Bone scintigraphy • and/or FCH-PET (post-treatment PET will be optional).	5 years
f) Overall survival	Overall survival	5 years
g) Quality of life	QLQ-C30 + QLQ-PR25	5 years
h) Optional ancillary biological study: validation of a novel mutational signature in patients with oligometastatic prostate cancer treated with radiotherapy		
INCLUSION CRITERIA	1) Histologically proven adenocarcinoma of the prostate 2) Patients aged 18 years or more 3) PS 0-1	

	4) Previous radical treatment to the prostate (radiotherapy or surgery) 5) PSA increase of at least 3 assays in the same laboratory over the last 12 months. 6) 1-5 pelvic lymph node metastases detected with 18FCH-PET. A relapse in the dressing prostatectomy is associated possible. 7) Upper limit of lymph node metastases: aortic bifurcation 8) Respect of dosimetry constraints to organs at risk 9) Treatment with hormone therapy may be started before inclusion, to a maximum of three months prior to Day 1 of radiotherapy. This hormone will necessarily be preceded by a free interval treatment of at least 6 months since the last injection, by adding the duration of action of this predictable injection (1, 3 or 6 months) 10) Patient affiliated to a social security scheme 11) Patient Information and written informed consent form signed
NON-INCLUSION CRITERIA	1) Bone or visceral metastatic relapse associated 2) Para-aortic nodal relapse (the upper limit is tolerated aortic bifurcation) 3) More than 5 lymph node metastases 4) Proof of metastases at initial diagnosis 5) Evidence of distant metastases in the pelvic lymph nodes or outside the prostate bed prior pelvic lymph nodes irradiation. Irradiation of the bed of the prostate is not an exclusion criterion, but the junction between prior irradiation bed prostatectomy and radiation field pelvic lymph nodes should be examined carefully 6) Castration resistance defined by clinical or biochemical progression despite a combined androgen blockade 7) Known contraindications to pelvic irradiation (eg, chronic inflammatory bowel disease, ...) 8) Known contraindications to hormone therapy, according to standard recommendations in force 9) Serious hypertension not controlled by appropriate treatment 10) Other concomitant cancer or history of cancer (within 5 years prior to study entry), except basal cell or squamous cell carcinomas of the skin. 11) Patient with a psychological, familial, sociological or geographical potentially hampering compliance with the study protocol and follow-up schedule 12) Patient already included in another interventional study involving the approval of a cpp during his screening for the study Oligopelvis 13) Private person of liberty or major trust

E) INVESTIGATIONAL TREATMENT DESCRIPTION

Experimental procedure

- **Radiation therapy**

A simultaneous integrated boost will be applied to PTVs. It will be administered 5 days per week during 5 to 7 weeks.

The radiation therapy will start three months (+/- 15 days) after the first injection of IADT.

General recommendations

The use of intensity-modulated radiation therapy (IMRT) is mandatory.

Irradiation will be delivered to patients with an empty rectum. It is recommended that the patient empties his bladder and rectum one hour before the planning CT scan and before each radiotherapy treatment, and then drink at least 1/3 L of water after voiding. The one-hour delay will be adapted to the patient's continence.

If the prostate bed has been previously irradiated, it is recommended that the irradiation be delivered with the bladder empty in order to avoid re-irradiation of the bladder due to overlapping fields.

Daily verification of patient's organ positioning using IGRT is mandatory.

The use of a record and verify processing software is mandatory.

Preparation of treatment

A planning CT of the pelvic cavity that includes all of the pelvic lymph nodes will be performed in the supine position, with intravenous contrast agent to aid visualization of the pelvic vessels. Oral contrast agent will also be administered to assist in the determination of the small bowel volume. The minimum CT resolution will be at least 3 mm thick slices every 3 mm, but thinner slices may be necessary for very small volume lymphadenopathy. Merging the CT with pelvic MRI may help to visualize the vascular axes and pelvic lymph nodes.
Fusion with FCH-PET (or PSMA-PET): The FCH-PET (or PSMA-PET) images will be segmented using a threshold adapted to the size of the lymphadenopathy. These images will be used to locate the pathological lymph nodes, but the tumor volume (GTV) will be contoured on the planning CT.

Target Volumes

a) Metastatic lymph nodes

GTV1 to GTV5 will be delineated on the planning CT-scan with the aid of FCH or PSMA PET.
A margin of 3-5 mm around the GTVs will define the clinical target volumes (CTVs).
An additional margin of 3-5 mm around the CTVs will define the planned target volumes (PTVs). The intersection between PTVs and small intestine will be removed from the PTVs.

b) Whole pelvic lymph node irradiation

Pelvic lymph nodes will be contoured according to the recommendations in the GETUG consensus statement (20). The pelvic lymph node CTV (PLN CTV) will include the common iliac, external iliac, internal iliac, pre-sacral (S1-S3) and obturator regions. 24The PLN CTV will be based on the pelvic vessels (arteries and veins) with an expansion of 7 mm, reduced where necessary at the bone, muscle, bowel and bladder boundaries. The upper limit is defined by the bifurcation of the abdominal aorta. If the prostate/prostate bed has been previously irradiated, the lower limit will be modified in accordance with the previous dosimetry in order to avoid overlap with regions which have received more than 20 Gy.
A margin of 5 mm around the PLN CTV will define the PTV. The intersection between PTVs and the small bowel will be removed from the PLN PTV

c) Prostate bed

Irradiation of the prostate bed will be considered if the prostate bed has not been irradiated.
The prostate bed CTV (PB CTV) will be defined according to the recommendations of the RTOG consensus (21).
Boundaries
Below the upper edge of the pubic symphysis, the prostate bed boundaries are:

- anteriorly: the posterior border of the pubic bone;
- posteriorly: the rectal wall;
- caudally: 8–12 mm below the vesicoureteral anastomosis;
- laterally: the levator ani and internal obturator muscle.

Above the upper edge of the pubic symphysis, its boundaries are:

- anteriorly: including 1–2 cm of the posterior wall of the bladder;
- posteriorly: the mesorectal fascia;
- cranially: the end of the vas deferens or 3–4 cm above the pubic symphysis;
- laterally: the sacro-recto-genito-pubic fascia.

A margin of 7mm will be added to the PB CTV to form the PB PTV.

d) PB relapse PTV

In case of prostate bed relapse, a PB relapse GTV will be defined based on PET-CT and MRI. A margin of 3-5 mm around the PB relapse GTV will define the clinical target volume (PB relapse CTV).
An additional margin of 3-5 mm around the PB relapse CTV will define the planned target volume (PB relapse PTV).

e) Organs at risk (OARs)

OARs will be contoured as recommended by the RTOG (22). No margin will be added (PRV) around organs at risk.

- Bladder: the outer contour of the bladder on all sections where it appears. The bladder volume is the volume between the outer contour and an inner contour that is defined 7mm from the outer contour.
- Rectum: the external contour of the rectum from the recto-sigmoid junction to the anal canal. The rectal wall is the volume between the outer contour and an inner contour that is defined 5mm from the outer contour.
- Intestine: the external contours of the sigmoid, colon and the small intestine are defined as an "intestinal bag" including the abdominal cavity as a whole. It will be important not to create areas of overlap between the intestine and the CTVs.
- Femoral head.

Dose prescription

A simultaneous integrated boost will be applied to the PTV1-5 and PLN PTV. The PB PTV will be treated using conventionally fractionated radiotherapy (2 Gy/fraction)

- PTV1-PTV5: 66 Gy in 30 fractions of 2.2 Gy
- PLN PTV: 54 Gy in 30 fractions of 1.8 Gy
- PB PTV: 63 Gy in 30 fractions of 2.1 Gy if the prostate bed has not been irradiated previously.
- PB relapse PTV: 66 Gy in 30 fractions of 2.2 Gy

Dose constraints

95 % of the PTV volumes will receive 95 % of the prescribed dose.
The QUANTEC recommendations advise that the maximum dose for the various organs at risk should be:

- Bladder: the bladder volume receiving a dose > 65 Gy will be no greater than 50 %.
- Rectum: V50 < 50%, V60 < 35%, V65 <2 5%.
- Bowel: the volume receiving 45 Gy will be less than 195 ml; V60<50 ml
- Femoral head: <5 % of each femoral head should receive a dose > 50 Gy.

Where the PTV coverage conflicts with the OAR constraints, OAR protection will be favoured, so the PTV may be reduced to the CTV.

Respect of dosimetric constraints to organs at risk. This is of major importance for patients with a past history of prostate/prostate bed irradiation delivering a maximum of 20 Gy to the metastatic pelvic lymph nodes

Image guidance

Image-guided radiotherapy (IGRT) will be performed daily. The daily registration will be based at least on bone structures. It will be possible to readjust to the nodal structures in case of displacements > 1 cm.

Quality control

A GETUG RT quality assurance committee has been established consisting of a radiation oncologist and a radiation physicist. This committee is available for consultation should questions arise concerning the treatment protocol. The committee will initially accredit each centre on the basis of an electronic copy of a single case plan that demonstrates:

- CTV and PTV contoured according to protocol;
- organs at risk (bladder and rectal walls and femoral heads) contoured according to protocol;
- DVH for intestine, bladder and rectal wall, PTV and CTV that meet dose constraints;
- a statement that patients will be treated with an approved daily image guidance technique.

All treatment plans will be sent via a web-based platform for central review and approval prior to beginning radiotherapy.

Quality control of IMRT: all IMRT plans will undergo quality assurance evaluation with ion chamber measurements or an equivalent method of dose verification to verify the absolute dose for each IMRT field, and film dosimetry to measure the relative dose for each IMRT field, as is standard clinical practice. An independent monitor unit calculation may be substituted for ion chamber dosimetry when available.

Management of previously irradiated patients

When the prostate/prostate bed has been irradiated previously, a cumulative dosimetric study will be performed to assess for radiotherapy volumes overlap, and the 20 Gy isodose will be drawn.
If any PTV1-5 has received more than 20 Gy during a previous course of irradiation, the patient should be excluded from the study.
If less than 20 Gy was delivered to PTV1-5, the lower limit of PLN PTV will be restricted to PTV1-5. No modification of the dose constraints will be applied.

Dose adjustment

No dose adjustments will be made.

- **Hormonotherapy**

Hormone therapy is recommended Eligard 45 mg acting for 6 months.
It will be ideally administered the day of start of radiation therapy or within 3 months before the first day of radiotherapy.

Nevertheless, free prescription is left to investigators.
When using other hormonal strategies (anti-androgen agonists, LHRH antagonists or LHRH), an administration for six months will be critical.

F) STATISTICAL CONSIDERATIONS	
SAMPLE SIZE DETERMINATION	It is difficult to accurately identify a control population. The recent adoption of FCH PET has enabled the detection of metastases in patients in biochemical relapse which the usual imaging modalities (bone scan, CT chest, abdomen and pelvis, pelvic MRI) were unable to detect. These patients therefore represent an intermediate group between patients with a rising PSA alone, and frank metastatic disease. To calculate the patient population, we can only rely on studies relating to a rising PSA patient population on one hand, and on first-line metastatic patients on the other hand. Prospective randomized data gathered from patients with a rising PSA showed that the median duration of biochemical control was 20 months with intermittent ADT [1]. Prospective randomized data concerning intermittent ADT in metastatic patients showed that 75 % of patients had resumed ADT after a mean duration of 15 months off [3]. Based on retrospective data, Ost et al. estimated that 51 % of patients are progression-free one to three years after salvage surgery or radiotherapy for pelvic oligometastatic disease [10]. Moreover, Rischke et al. showed a 50 % clinical recurrence at 2 year for patients undergoing both salvage lymphnode dissection and pelvic radiotherapy [18]. We therefore estimate that a biochemical relapse-free survival at 2 years of 70 % would be a significant result. Based on a one-step Fleming design [19], we wish to be 95 % ($\alpha < 5$ %) certain that any difference observed between the standard and experiment treatment groups is not due to the play of chance. We also want to be able to detect such a difference with 95 % power (b = 5 %). With these α and b, rejecting the null hypothesis H0: $\Pi \leq 50$ %, and accepting the alternative hypothesis H1: $\Pi \geq 70$ %, will require 63 evaluable patients.

	Around 10 % of patients may be lost to follow-up before the evaluation of biochemical relapse at 2 years, so to ensure that we retain at least 63 patients until this evaluation it will be necessary to recruit 70 patients to this study. If 39 or more of these 63 evaluable patients are still free of biochemical relapse at 24 months, we may reject the null hypothesis H0: $\Pi \leq 50$ % with a risk of error of 3.85 % and a power of 93.5 % to detect the alternative hypothesis H1: $\Pi \geq 70$ %.
DESCRIPTION OF ANALYSIS SETS	The statistical analysis will be conducted with SAS 9.4 (Institute Inc., Cary, NC, USA), Stata 13.1 Special Edition (StataCorp LP, College Station, Texas, USA). For all analyses, a p-value of less than 0.05 was considered as statistically significant. All reported p-values are two sided. **Description of analysis sets** Data from all evaluable patients will be analyzed. **Descriptive statistics** A descriptive analysis of the patients included will be carried out. This analysis will include point estimates, numbers and percentages for qualitative variables, and mean, standard deviation, median, quantiles and range for quantitative variables. **Analysis of safety endpoints** If a patient presented the same toxic event several times, only the higher grade event was analyzed. **Analysis of survival endpoints** The different survival endpoints were analyzed are defined as follows: Progression-free survival (PFS): time from randomization until biochemical-clinical failure or death from any cause. The definition of a biochemical-clinical failure is detailed in section 8.5.1. Overall survival (OS): time from randomization until death from any cause. Patients for whom the event will not occur during the follow-up period will be censored at their last follow-up date. For PFS and OS, the determination of survival curves will be performed by means of Kaplan-Meier method. **Analysis of quality of life scoring** Quality of life scores were compared between baseline and 6 months, and between baseline and 12 months using a Wilcoxon signed test for matched pairs. A Benjamini-Hochberg procedure was applied to control for false discovery rate. Quality of life differences were considered as clinically relevant when greater than 10. **Statistical criteria for stopping the study** An analysis of acute toxicity persisting at one month after radiotherapy will be performed after the inclusion of the 20th patient to ensure that the toxicity of the irradiation protocol is not higher than expected. If, among the first 20 patients, 10 or more patients present with grade 2 toxicity, we can state that the rate of grade 2 complications is greater than the reference norm of 30 % ($p = 0.048$). In this case the Data Safety Monitoring Board (DSMB) will meet to analyze the toxicity and decide whether to continue the study. If, among the first 20 patients, 2 or more patients present with grade 3 toxicity, we can state that the rate of grade 3 complications is above the reference norm of 2 %

	(p = 0.059). In this case the DSMB will meet to analyze the toxicity and decide whether to continue the study.

G) STUDY CALENDAR	
DURATION OF INCLUSION PERIOD	24 months
TREATMENT DURATION	ADT + IG-IMRT: 6 months of ADT / 6 to 7 weeks (30 fractions) of IG-IMRT
POST TREATMENT FOLLOW UP	10 years
PRIMARY ENDPOINT ANALYSIS EXPECTED DURATION	2 years
STUDY COMPLETION DURATION (INCLUDING FU PERIOD)	12,5 years

SCHEDULE OF STUDY ASSESSMENTS

Visits	Inclusion	Treatment period	follow-up			
Visits	Max 2 months prior to RT day 1		M1 1 month after end of RT	Before progression: Every 6 months during 2 years	Before progression: Every 6 months until progression	After progression: Every 6 months until death
Inclusion/exclusion criteria	X					
Signed consent form	X					
Inclusion (max 2 months prior to RT)	X					
FCH PET	X (a)					X (b)
Physical examination with PS	X	X (d)	X	X	X	X
Prior history, tumor characteristics	X					
Blood Pressure	X	X (d)	X	X		
Acute toxicity during ADT and RT (f)		X (d)	X			
Late toxicity (f)				X		
QLQ-C30 et QLQ-PR25	X		X	X		
PSA	X		X (f)	X (f)	X (f)	
Testosterone	X (g)		X	X	X	
ADT (c) + RT		X				

(a) maximum 3 months prior to initiation of ADT
(b) at progression
(c) 6 months treatment staring on RT day 1 or maximum 3 months prior to RT
(d) once per week during RT
(e) biochemical progression = PSA higher than inclusion PSA with 2 successive rises in the same laboratory
(f) NCI-CTCAE v4.0
(g) 28 days prior to ADT

STUDY DIAGRAM