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DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE
(D.E.S. Oncologie Option: Radiothérapie)

par

Loïg VAUGIER

présentée et soutenue publiquement le 5 octobre 2020

Etude OLIGOPELVIS
Place de la radiohormonothérapie pelvienne de rattrapage en situation de récidive oligométastatique ganglionnaire de cancer prostatique hormononaif

Président et Directeur de thèse : Monsieur le Professeur Stéphane Supiot

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Combined Salvage Pelvic Radiotherapy with 6-Month Hormone Therapy in Nodal Oligorecurrences of Castration-Sensitive Prostate Cancer

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A ma famille et belle-famille, mes parents, grands-parents, mes soeurs, neveux ou nièce : c'est fait !

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Enfin, à toi, Mathilde, Jeanne, Malo et Madeleine, sans qui je n'aurais pu ni prendre ni suivre ce chemin tout de même un peu tortueux.

Valorisation médico-scientifique

Ce travail a déjà fait l'objet:

- d'une publication en 2019 dans le journal *International Journal of Radiation Oncology, Biology, Physics* (IF : 6,2 en 2018)
  Early Toxicity of a Phase 2 Trial of Combined Salvage Radiation Therapy and Hormone Therapy in Oligometastatic Pelvic Node Relapses of Prostate Cancer (OLIGOPELVIS GETUG P07)
  doi: 10.1016/j.ijrobp.2018.12.020
- d'un poster au congrès de European Society for Radiotherapy Oncology (ESTRO) en 2018

Les résultats généraux de l'étude ont été soumis à publication dans le journal *Lancet Oncology*.

L'analyse du type de rechute à progression a été soumise à publication en tant que "short communication" dans le journal *International Journal of Radiation Oncology, Biology, Physics*.

Une analyse quantitative de la dosimétrie cumulée des patients ayant eu un traitement de radiothérapie pelvienne de rattrapage précédée d'une radiothérapie de loge prostatique, est en cours. L'objecfif sera d'établir la dose délivrée en recoupe par la réirradiation et de l'associer aux données de toxicité.

ABSTRACT

BACKGROUND

Oligorecurrent pelvic nodal relapse of prostatic cancer is a challenge for regional salvage treatments. Androgen deprivation therapy (ADT) is a mainstay in metastatic prostate cancer but salvage pelvic radiotherapy may offer ADT-free periods for patients with regional nodal relapses.

METHODS

We did an open-label, phase II trial of combined high-dose intensity modulated radiotherapy and ADT (6 months) in oligorecurrent (≤ 5) pelvic node relapses of prostate cancer as detected by Flurocholine PET-CT imaging. The prescribed dose was 54 Gy in 1.8 Gy fractions with up to 66 Gy in 2.2 Gy fractions to the pathologic pelvic lymph nodes. The primary endpoint was the 2-year progression-free survival (PFS). Progression was defined by PSA above the level at inclusion and/or clinical evidence of progression as per RECIST 1.1 and/or death of any cause. Secondary objectives were biochemical relapse-free survival (BRFS), overall survival (OS), time to start a second line treatment (TTST), time to start of palliative ADT (TTADT), acute and late toxicity, and quality of life assessed by EORTC QLQ-C30 and PR25 questionnaires.

FINDINGS

Between August 2014 and July 2016, 67 patients were recruited in 15 centers. Around half of them had received prior prostatic irradiation. Median age was 67.7. After a median follow-up of 37.8 months, the 2-year PFS rate was 79.1%. Median PFS was 45.3 months. Median BRFS, TTST and TTADT were 25.9, 48 and 51.9 months, respectively. At 3 years, 44.8% of patients achieved a biochemical complete response. 3-year OS was 93.1%. Grade 2+ 2-year genitourinary and gastrointestinal toxicity were 10% and 6% respectively. Patients with prior prostate bed irradiation did not exhibit increased toxicity. EORTC questionnaire scores did not worsen significantly with time. Around half of clinical relapses were para-aortic lymph nodes, one third were bone metastases. Pelvic recurrences (14.5%) were limited. 27% patients were progressive with ≤ 3 detected metastases. ADT and stereotactic radiotherapy were performed in 52.5% and 32.5% patients respectively.

INTERPRETATION

Combined high-dose pelvic salvage radiotherapy and ADT allowed for prolonged tumor control in oligorecurrent pelvic node relapses of prostate cancer with limited toxicity, even in patients with a past history of prostatic irradiation. Approximatively 45% patients were in biochemical complete response after 3 years and almost 30% patients remained oligometastatic at further progression.

KEYWORDS: pelvic radiotherapy; oligometastatic prostate cancer; PET-guided IMRT

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Chapter 1

Introduction

The major cause of death among prostate cancer patients is the development of metastases [Hamdy *et al.* (2016)]. The development of new imaging techniques based on prostate cancer-specific markers such as fluorocholine (FCH), Prostate-Specific Membrane Antigen (PSMA) or Fluciclovine positron emission tomography (PET) has made identification of limited metastatic relapses of prostate cancer feasible, especially in small pelvic lymph nodes (PLN) [Colombié *et al.* (2015), Calais *et al.* (2019), Lépinoy *et al.* (2014), Supiot and Rousseau(2019)]. Among the various oligometastatic scenarios - a limited number of metastases (e.g. $\leq$5 bone and/or lymph node metastases, with no visceral involvement) after previous prostate treatment - a PLN relapse is a paramount challenge as an apparent turning point between still-controllable locoregional disease that can be managed without continuous androgen blockade (through with salvage therapeutics) and diffuse disease for which androgen blockade would be the most appropriate treatment [Tosoian *et al.* (2017), Ost *et al.* (2018)]. Oligorecurrent prostate cancer is now the preferred term for designing such limited metastatic progression at the hormone sensitive state [Guckenberger *et al.* (2020)].

In locally advanced disease, the role of radiotherapy in the management of micrometastatic lymph nodes is highly debated [Pommier *et al.* (2016), Roach *et al.* (2018)]. In the salvage post-prostatectomy setting, there is a further lack of clear evidence about the role of radiotherapy to the lymph nodes [Spiotto *et al.* (2007)]. Metastases-directed therapy using stereotactic radiotherapy (SBRT) to the identified lymph nodes is one option, which was shown to be feasible, well-tolerated and able to delay the need for ADT [Ost *et al.* (2018), Siva *et al.* (2018), Phillips *et al.* (2020)]. However, most patients relapse in the pelvic area [Ost *et al.* (2016b), Deek *et al.* (2020)]. Salvage elective whole pelvis radiation therapy (EWPRT) with an additional boost to any PET-positive PLN is one attractive option with the advantage of tackling potential pelvic micrometastases at the same time. The best current evidence of the benefit of such EWPRT is derived from retrospective studies on heterogeneous populations with heterogeneous treatment plans [Schick *et al.* (2013), Picchio *et al.* (2014), Fodor *et al.* (2017), Tran *et al.* (2018), Ingrosso *et al.* (2020), Sato *et al.* (2020)].

The main objective of the multicenter phase 2 trial - OLIGOPELVIS-GETUG P07 - was to assess the efficacy of high-dose salvage EWPRT in a prospective manner in a well-defined population. Prior prostatic irradiation was allowed. We hypothesized that such EWPRT combined with 6-month ADT would achieve a 2-year progression-free survival of 70%. Here we present the main objective of the trial after a minimum follow-up of 3 years, as well as the pattern and treatment at further progression.

Chapter 2

Materials and Methods

2.1 Study design and participants

The complete OLIGOPELVIS-GETUG P07 trial design has already been published [Supiot *et al.* (2015)]. Inclusion criteria were pelvic (below the aortic bifurcation) oligorecurrent castration-sensitive prostate cancer patients with less than 6 metastatic PLN detected by FCH-PET. If ADT had been previously administered, a minimum of 6 months wash out period was required and serum testosterone had to be higher than 6 nmol/L prior to inclusion. Prior irradiation of the prostate or the prostate bed (PB) was allowed with a minimum 1 cm gap between prostate and salvage pelvic radiotherapy fields. Patients with extra-pelvic metastases or patients under active ADT were excluded.

The trial population was divided into four groups, each with a different treatment plan (see Fig. 2.1 for planning doses): (1) Group A: patients with prior radical prostatectomy (RP) and no prior PB radiation; (2) Group B: the same as group A, but with an FCH- PET positive signal in the PB, suggesting local relapse; (3) Group C: with both previous radical prostatectomy (RP) and salvage prostate bed radiation therapy (PB-RT), thus entering a second round of salvage therapy; and (4) Group D: with prior conservative prostate treatment (external body radiation therapy or brachytherapy).

2.2 Procedures

Image-guided intensity-modulated radiation therapy (IG-IMRT) was required to deliver 54 Gy in 1.8 Gy fractions to the whole pelvis, with a simultaneous integrated boost of 66 Gy in 2.2 Gy fractions to the pathologic PLN. Patients who had not received prior irradiation received 66 Gy in 2 Gy fractions to the PB, with up to 72 Gy in 2 Gy fractions in the case of PB local relapse. A radiotherapy quality assurance committee from the Groupe d'Etudes des Tumeurs Uro-Génitales (GETUG) and consisting of a radiation oncologist and a radiation physicist initially accredited each centre on the basis of an electronic copy of a single case plan. Volumes were delineated according to the Radiation Therapy Oncology Group (RTOG) international guidelines [Lawton *et al.* (2009)], but for the whole pelvis clinical target volume, the upper limit was defined by the aortoiliac bifurcation as suggested by the GETUG recommendations [Sargos *et al.* (2015)]. Inguinal, peri-vesical and para-rectal regions were not treated by prophylactic radiation.

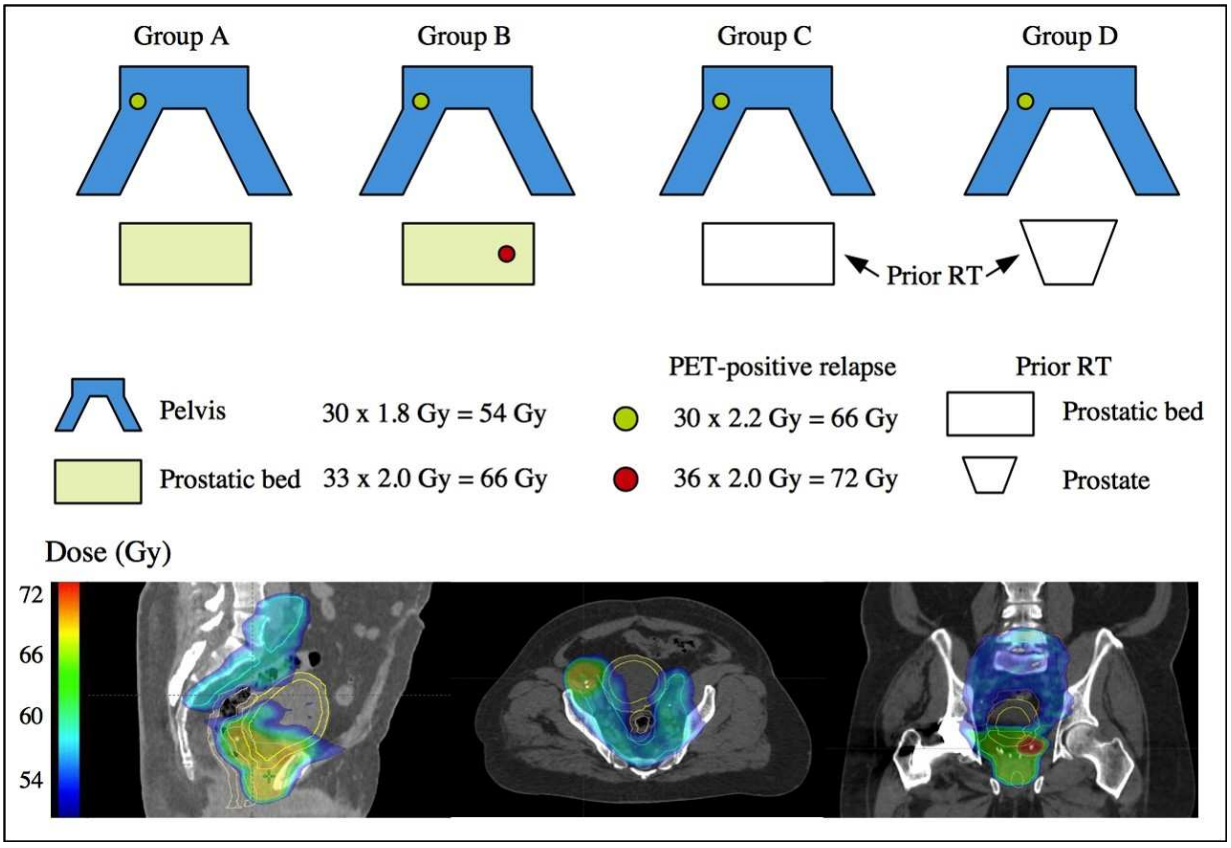

Figure 2.1: Top panel: schematic view of the patient population and treatment planning options. Prior RT for Group C: prior radiotherapy of the prostatic bed. Prior RT for Group D: prior prostate radiotherapy (external beam or brachytherapy). Bottom panel: Example of the treatment planning for one patient of Group B with FCH-PET positive node into the right external iliac vessels and one left-posterior local relapse into the prostatic bed. Delineations of whole pelvic lymph nodes, bladder and rectum walls are shown.

Androgen blockade was achieved by Luteinizing Hormone Releasing Hormone (LH-RH) agonist or antagonist injections for 6 months, ideally administered on the first day or within the 3 months before the first day of radiation therapy.

2.3 Radiation control quality

All radiotherapy plans were centrally reviewed by one radiation oncologist. Number of FCH-PET positive PLN, total gross tumor (GTV), clinical target (CTV) and planning target (PTV) volumes were documented for all patients. Major deviation to the protocol was retrospectively defined by: either the minimal dose covering the PTV (D98) for FCH-PET positive PLN or whole pelvis was less than 90% of the prescribed dose and/or the upper limit of the CTV for the whole pelvis was found under the aortoiliac bifurcation or the intervertebral L4/L5 level. The dose covering 25% and 50% of the bladder and rectum walls were also recorded in order to further analyse the potential radioinduced toxicity. These dosimetric data were compared and contrasted based on prior (patients of Groups C+D) or not (patients of Groups A+B) prostate or prostatic bed radiotherapy.

2.4 Outcomes

The primary objective of this study was to describe the 2-year progression-free survival (PFS). Progression was defined by a cluster of events including: PSA progression defined as two consecutive PSA levels above the level at inclusion and measured in the same laboratory; and/or clinical evidence of progression as per RECIST 1.1 [Eisenhauer *et al.* (2009)]; and/or death of any cause.

Secondary objectives included biochemical relapse-free survival (BRFS), overall survival (OS), time to start a second line treatment (TTST), time to start of palliative ADT (TTADT), acute and late toxicity, and quality of life assessed by EORTC QLQ-C30 and PR25 questionnaires. Biochemical relapse was defined as two consecutive PSA levels higher than 0.2 ng/mL following the post-treatment Nadir. For patients with prior conservative prostate treatment (external beam radiotherapy or brachytherapy), biochemical relapse was defined as i) a PSA > 0.2 ng/mL following the post-treatment Nadir; and ii) PSA level higher than the Nadir following the prior conservative prostate treatment. Toxicity (CTCAE v4) and quality of life were evaluated prior to treatment and one month after completion of radiotherapy, and then every 6 months for 2 years. Acute toxicity was defined as events occurring between the first week of EWPRT and 1 month after the end of EWPRT (M1), while events occurring after M1 were documented as late toxicity. If a patient presented with the same toxic event several times, only the highest grade event was reported. Toxicities were recorded until the progression as defined above. PSA and testosterone levels were determined prior to radiotherapy, 1 month after completion, every 6 months for 2 years and then yearly until progression.

2.5 Pattern progression analysis

Under-diaphragmatic nodal relapses were centrally segmented on the computed tomography (CT) coupled to FCH- or PSMA-PET. The segmentation was performed jointly by one radiation oncologist and one

nuclear physician. The TEP-CT was then registered to the pretherapeutic CT used for the EWPRT ± prior PB-RT dose planning. The minimal relapsing dose (DR_{min}) - corresponding to the minimal dose that was delivered to the nodal relapse revealed by PET at further progression - was defined by the dose covering 98% of the relapsing volume as segmented on PET-CT. Radioresistant (geographic-missed) nodal recurrences were defined as PET-positive nodes covered i) with $DR_{min} \geq (<)$ 50 Gy and ii) by either EWPRT or prior PB-RT. We did not perform cumulative dose summation at this level.

2.6 Statistical analysis

A one-step Phase 2 Fleming design was applied. Based on the hypothesis of a 2-year PFS rate of 70 % with salvage pelvic lymph node IG-IMRT combined with 6-month ADT, 63 evaluable patients would enable to demonstrate with a power of 93.5% and an alpha risk of 4% that the 2-yr PFS rate is >50% [Supiot *et al.* (2015)]. A target sample size of N=70 was then calculated to account for a 10% drop out rate.

Data from all evaluable patients were analyzed. PFS, BRFS, OS, TTST and TTADT were computed from beginning of treatment. Clinical progression-free survival (CPFS) was defined as the time from beginning of treatment to clinical evidence of progression as defined above. The Kaplan-Meier method was applied to estimate survival curves. We used Cox regression assuming proportional hazards to run post-hoc univariate analyses in order to investigate the prognostic value on PFS of PSA level at baseline, Gleason score at diagnosis, number of PLN, PSA level 6 months after treatment initiation, PSA doubling time (PSADT), time from prostate cancer diagnosis to the initiation of the treatment under study. We estimated hazard ratios (HRs) and their 95% CIs. Univariate logistic regressions were performed as post-hoc analyses to assess the prognostic value on under-diaphragmatic nodal recurrence of: PSA level at baseline, Gleason score at diagnosis, number of PLN, PSA doubling time (PSADT), time from prostate cancer diagnosis to the initiation of the treatment under study, total PLN GTV and CTV. We did not impute missing data for covariates.

18-month and 24-month quality of life scores were compared with baseline scores using a Wilcoxon signed test for matched pairs. P values were corrected according to a Benjamini-Hochberg procedure to control for false discovery rate. Quality of life differences were considered as clinically relevant when greater than 10. All p values were based on two-sided tests and were considered significant if less than 0.05. We used SAS version 9.4 for analyses.

The trial was registered, number NCT02274779.

Chapter 3

Results

3.1 Patient numbers and characteristics

Seventy-five patients in 15 French oncology centers were assessed for eligibility from August 2014 until July 2016 (Fig. 3.1). One patient was excluded at screening because of previous irradiation and incompatibility for dosimetric constraints. Among the seventy-four patients that were included in the study, seven patients were excluded for various reasons (lost at follow-up: 1; more than 5 pathological PLN: 1; time between ADT and RT > 3 months: 2, unacceptable PSA follow-up: 3). The remaining sixty-seven patients were analyzed.

Patient characteristics and staging at diagnosis are summarized in table 3.1 and 3.1. Median age was 67.7 $\pm$ 6.5 years. Sixty-one patients (91%) were initially treated by RP (groups A, B and C). Only one had documented PLN involvement (pN1) at prostate cancer diagnosis. Thirty patients (44.7%) received first-line salvage PB-RT (group C). Only a minority of the patients (9%, 6/67) had been previously treated conservatively (Group D): three were treated with external beam radiotherapy at a mean dose of 74 Gy (70-76 Gy) and three had received prostate brachytherapy. A huge majority (85%) of patients had one (61%) or two (24%) positive PLN (Tab. 3.1). Four patients (group B) had a concurrent local relapse in the PB.

At the inclusion, patients had mostly ECOG performance status 0 and had no digestive comorbidities or any history of abdominal surgery other than RP. Almost half were hypertensive. Thirteen of the 67 patients (19.4%) had minor urinary symptoms at baseline (mostly grade 1, only one with grade 2), corresponding to urinary urgency and incontinence. Two of the 67 patients (3%) had grade 1 global bowel discomfort and diarrhea.

3.2 Radiation control quality

Dosimetric data for all patients were retrospectively reviewed. For all patients, 95% of the PTV was covered by at least 95% of the prescribed dose as required. Fourteen patients (21%) had a major deviation to the protocol as *a posteriori* defined: five patients for the FCH-PET positive PLN or whole pelvis dose

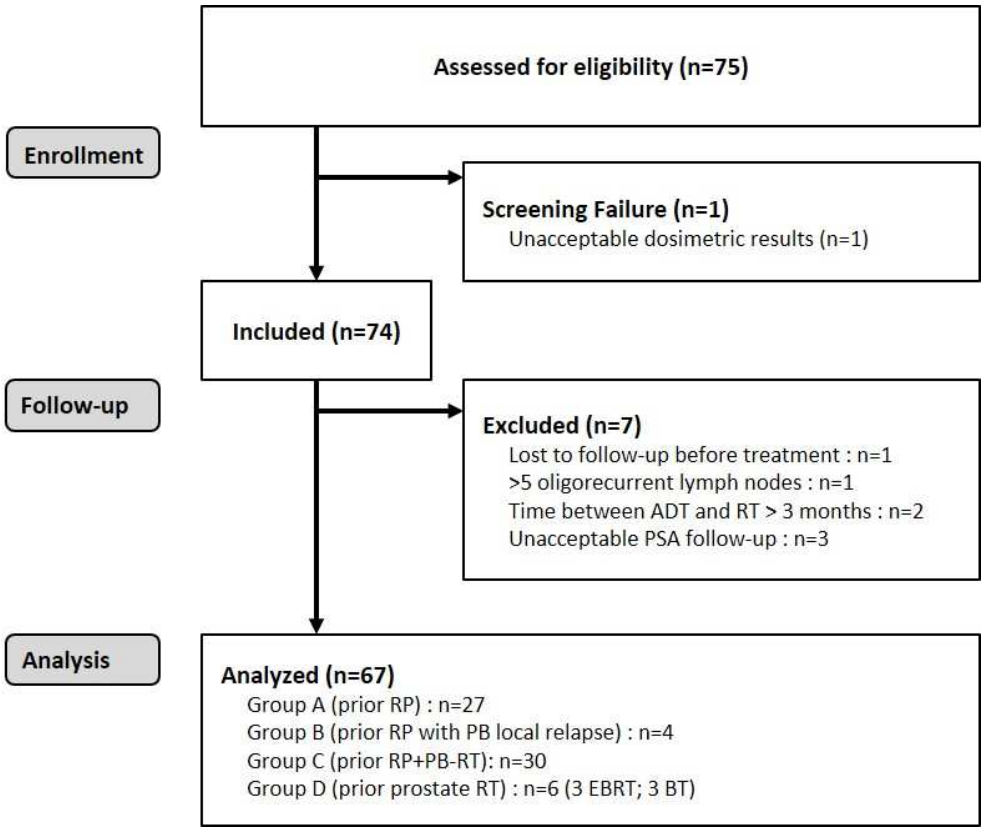

Figure 3.1: Trial flow-chart. RP = radical prostatectomy; PB = prostatic bed; (EB)RT = (external beam) radiotherapy; BT = brachytherapy.)

Table 3.1: Initial prostatic adenocarcinoma staging (TNM 2005) and baseline characteristics of the patients. RP (radical prostatectomy); PB (prostatic bed); EBRT (external-beam radiotherapy); BT (brachytherapy); PLN (pelvic lymph node). Digestive comorbidities : gastric ulcer, gastro-esophageal reflux, colonic polyps. Quantitative variables : mean ± standard deviation. Qualitative variables : number of subjects (%).

	(n = 67)
Initial prostate staging	
Gleason score	7 ± 0.8
Pathological tumour stage	
pT1	2 (3.0%)
pT2	24(35.8%)
pT3	35 (52.2%)
cT1	3 (4.5%)
cT2	3 (4.5%)
Pathological node involvement	
pN0	52 (77.6%)
pN1	1 (1.5%)
Nx	14 (21.0%)
Prior prostate treatment	
Group A (RP)	27 (40.3%)
Group B (RP)	4 (6%)
Group C (RP+PB-EBRT)	30 (44.8%)
Group D (prostate conservative)	
EBRT	3 (4.5%)
BT	3 (4.5%)
Baseline characteristics	
Age (years)	67.7 ± 6.5
PSA (ng/mL)	3.7 (IQR: 1.5-5.6)
ECOG Performance Status	
0	62 (92.5%)
1	5 (7.5%)
Hypertension	
yes	32 (47.8%)
unknown	1 (1.5%)
Tobacco	
yes	6 (9.0%)
unknown	13 (19.4%)
Diabetes	
yes	11 (16.4%)
unknown	1 (1.5%)
Digestive comorbidities	
yes	7 (10.4%)
unknown	1 (1.5%)
Prior abdominal surgery	
yes	15 (22.4%)
unknown	1 (1.5%)

Table 3.2: Oligorecurrent prostate cancer characteristics at baseline depending on prior (patients of Groups C+D) or not (patients of Groups A+B) prostatic bed radiotherapy (PB-RT). PLN = pathologic pelvic lymph nodes. Quantitative values: median [range].

	Total	**Groups A+B**	**Groups C+D**
Patients with FCH-PET-positive PLN	67	31 (46.3%)	36 (53.7%)
1 PLN	41 (61%)	19	22
2 PLN	16 (24%)	7	9
3 PLN	6 (9%)	2	4
4 PLN	3 (4.5%)	2	1
5 PLN	1 (1.5%)	1	-
Number of FCH-PET-positive PLN	122	62	60
Time with prior PB-RT (months)		-	54 [10.5-144]
Time with primitive diagnosis (months)		53.5 [33-129]	91 [28-168]

covering (4 with prior PB-RT; Table 3.2) and ten because of an unsatisfactory pelvis delineation, e.g. the superior border of the CTV was the L5/S1 intervertebral level. One patient had both deviations.

There were however no significant differences for the PTV dose covering depending on prior radiotherapy or not (Fig. 3.2 and Table 3.2). A notable lower dose was delivered to the bladder and rectum walls for patients with prior radiotherapy (Table 3.2). This was due to the prophylactic prostatic bed irradiation performed in the same time than EWPRT for the patients without prior PB-RT (Fig. 2.1).

3.3 Toxicity and quality of life

Acute genitourinary toxicity (Tab. 3.3) was dominated by grade 1 urinary urgency (33 of 67 patients, 49.2%) (Fig. 3.3). Grade 2+ 1- and 2-year genitourinary events yielded 10.5% [7/67] and 10% [5/50], respectively. Three patients (3 of 67 patients, 4.5%) suffered from severe grade 3 urinary incontinence at 1 year and two (2 of 50 patients, 4%) at 2 years following EWPRT; 1 of whom had isolated grade 3 hematuria, leading to the discovery of a bladder papillary carcinoma (pTa).

Around 67% of the patients (45 of 67) were affected by acute moderate diarrhea: 55.2% (37 of 67) grade 1 and 11.9% (8 of 67) grade 2 (Fig. 3.3). Around 34% of the patients (23 of 67) reported moderate grade 1 abdominal pain, constipation, bloating, or flatulence. At 1 and 2 year, grade 2+ GI toxicity were 6% (4 of 67) and 6% (3 of 50), respectively. Of note, no patient suffered from chronic grade 2 diarrhea or intestinal bleeding.

Pooling the patients who had not previously undergone RT (groups A and B) versus the others (groups C and D), there were no notable differences regarding the acute or later toxicity (Fig. 3.3). There were no cardiovascular events, but a moderate worsening of hypertension was noted.

Regarding the quality of life evaluation: The completion rate for the quality of life questionnaires yielded 67% and 54% at 18 and 24 months respectively. There were no significant alteration in urinary or

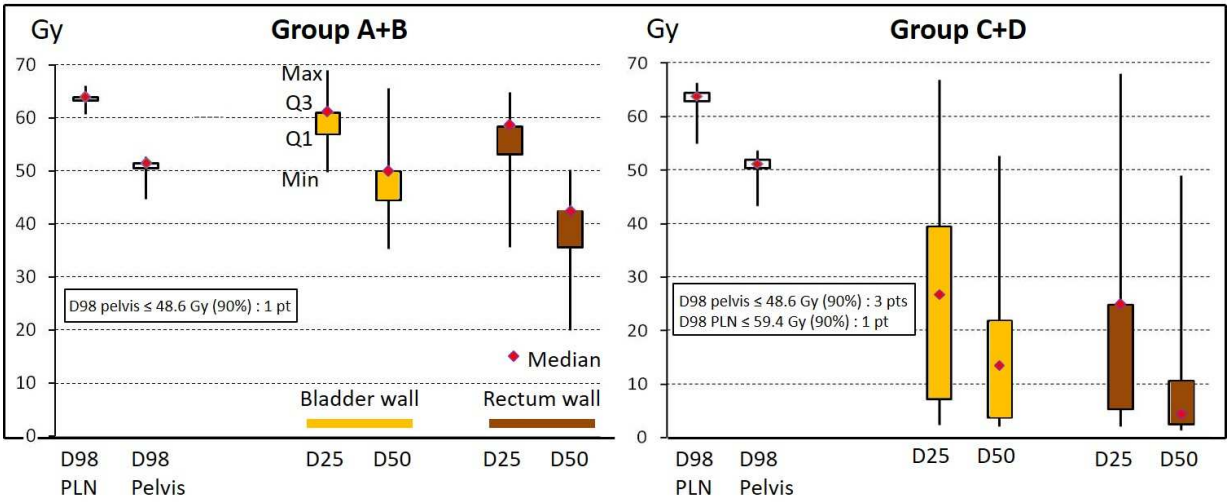

Figure 3.2: Control quality for the dose delivered to the planning target volumes (PTV) of the PET-positive pelvis lymph nodes (PLN) and the prophylactic whole pelvis for patients without (Groups A+B) or with (Groups C+D) prior radiotherapy. D98 corresponds to the dose (Gy) covering 98% of the PTV.

Table 3.3: Radiation control quality. Patients of Groups C+D had received prior prostatic bed radiotherapy (PB-RT). PLN = pathologic pelvic lymph nodes; GTV = gross tumor volume; CTV = clinical target volume; PTV = planning target volume; Dx = dose covering x% of the volume. Quantitative values: median [range].

	Groups A+B	**Groups C+D**
FCH-PET positive PLN		
GTV (cm^3)	2.5 [0.5-20]	2.5 [0.5-18]
CTV (cm^3)	12.5 [4.5-82]	15.5 [4.5-45]
PTV (cm^3)	37.5 [20-144.5]	40.5 [16.5-88]
D98 PTV PLN (Gy)	64 [60.5-66]	64 [55-66.5]
D98 PTV pelvis (Gy)	51.5 [44.5-52.5]	51 [43.5-53.5]
Bladder wall		
D25 (Gy)	61 [50-69]	26.5 [2.5-67]
D50 (Gy)	50 [35.5-65.5]	13.5 [2-52.5]
Rectum wall		
D25 (Gy)	58.5 [35.5-65]	25 [2-68]
D50 (Gy)	42.5 [20-50.5]	4 [1.5-49]

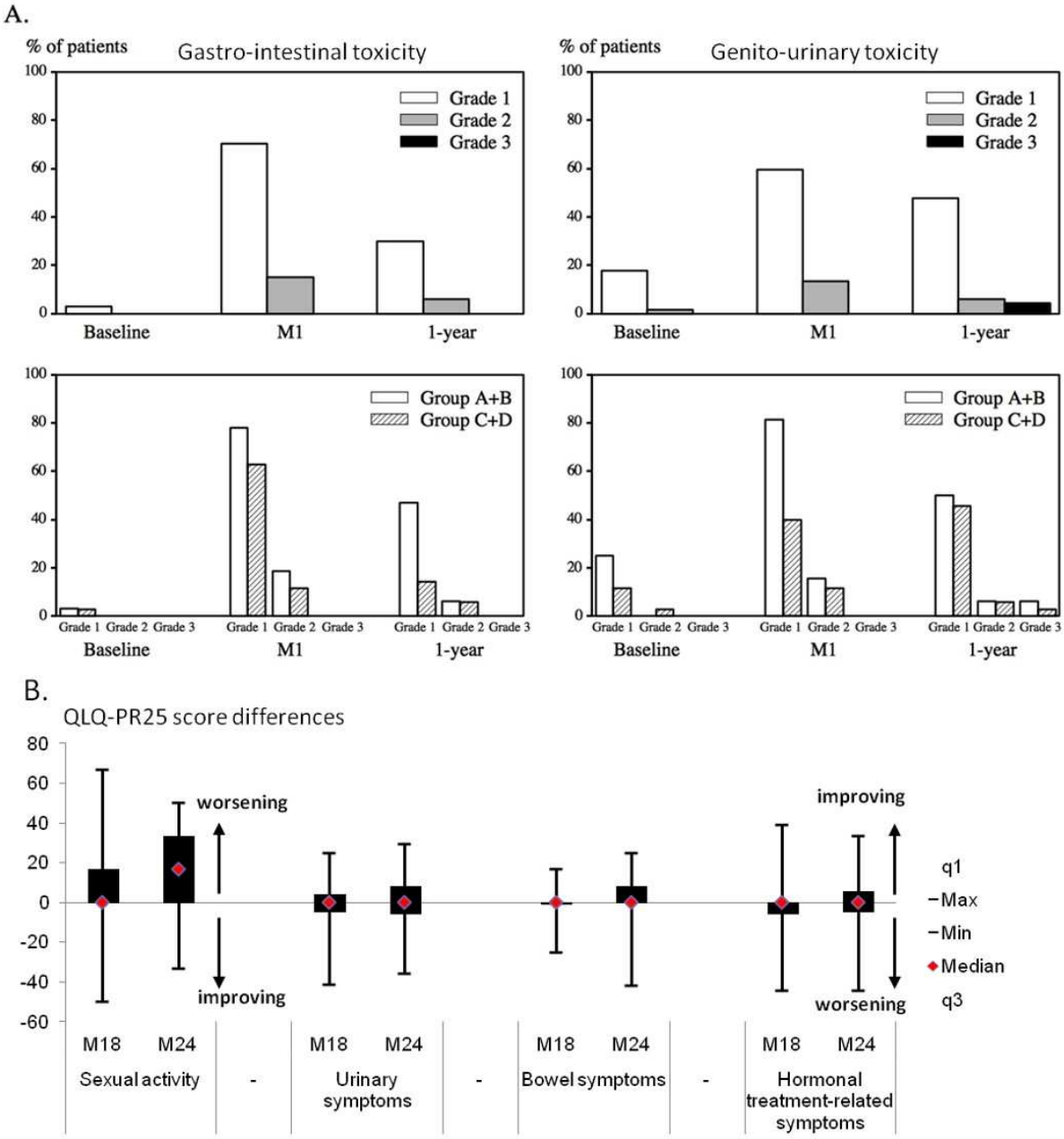

Figure 3.3: Panel A: Number of patients with gastrointestinal (left) and genitourinary (right) CTCAE v4 toxic events at M1 ($\leq$ 1 month after the end of radiotherapy) and one year after the end of radiotherapy. The number of patients with urinary and bowel troubles at baseline are given for comparison. Patients of Group A and B did not receive prior radiotherapy; patients of Group C and D respectively received prior prostatic bed and prostate exclusive radiotherapy. Panel B: QLQ-PR25 score differences with time.

Table 3.4: Number of patients with acute ($\leq$ 1 month after the end of radiotherapy) and 2-year CTCAE v4 toxicity. No grade 4 were reported. If a patient presented with the same toxic event several times, only the highest grade event was reported.
Others = arterial hypertension in the vast majority.

CTCAE Grade						
	1		2		3	
Adverse effect category	n	%	n	%	n	%
Gastrointestinal						
Acute	47	70%	10	15%	-	-
2-year	15	30%	3	6%	-	-
Genitourinary						
Acute	40	60%	9	13.5%	-	-
2-year	18	36%	3	6%	2	4%
Sexual troubles						
2-year	2	4%	4	8%	1	2%
Others						
Acute	12	18%	31	46%	12	18%
2-year	23	46%	2	4%	-	-

intestinal quality of life (p =1.0000 and p = 0.5726, respectively) for the QLQ-PR25 scores at 1 year or later (Fig 3.3). Testosterone levels went back to normal levels in all patients except 1 after a median time of 13 months. Hormonal treatment related quality of life was maintained at 2 years, but sexual quality of life decreased. There were no significant changes among the items of the QLQ-C30, in particular to physical or cognitive functioning (Fig. 3.4). Dyspnea and role functioning were the only symptoms to worsen to a not clinically relevant level but statistically significant degree between baseline and 6-month (p =0.0260 and 0.0468, respectively), symptoms resolved at one year.

3.4 Systemic oncologic outcomes

The median follow-up was 37.8 months (range, 8.5 months to 61.7 months). The 2- and 3 year PFS rate was 79.1% and 56.3%, respectively (Fig. 3.5). Median PFS was 45.3 months (95% CI: 31.8-48.5 months). Progression was clinical and biochemical in 52 and 7.5% respectively. Median BRFS was 25.9 months (95% CI: 20.9-41.8 months, Fig. 3.6). At 2 and 3 years, 56.7 and 44.8% of patients achieved a persisting complete biochemical response respectively. The 2- and 3-year TTST was 82.0% and 60.7% respectively (Fig. 3.6). Median TTST was 48.0 months (95% CI: 35.6-53.6). Median TTADT was 51.9 months (95% CI: 41.0-53.6, Fig. 3.7). The 3-year OS rate was 93.1% with 1 prostate cancer-related death at 33 months after the beginning of treatment. No prognostic factor could predict for progression or complete response (Table 3.4). Lower PSA value than 0.5 ng/mL at M6 was significantly correlated with better PFS (HR 8.4, $p < 0.001$).

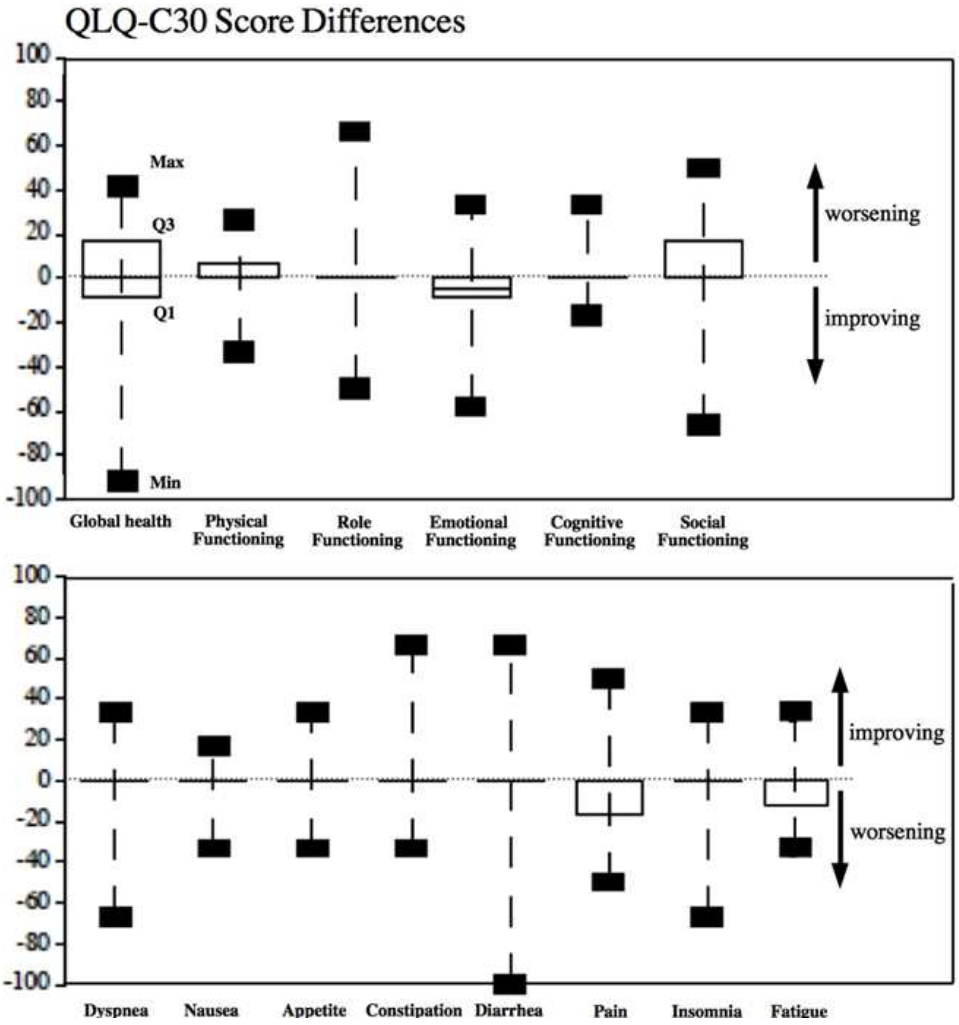

Figure 3.4: QLQ-C30 score differences between baseline and 1-year following the treatment under study.

3.5 Patterns of progression

With the median follow-up of 37.8 months, 35/67 (52%) patients have presented clinical progression, while 5/67 (7.5%) had biochemical progression only. Median CPFS was 45.9 months [95% CI: 39.6-61.5]. Median PSA at clinical progression was 3.9 (IQR: 2.4-4.9) ng/mL. Clinical progression was assessed by FCH-PET for 26/40 (65%) progressive patients, ^{68}Ga-PSMA-PET for 6/40 (15%), thoraco-abdomino-pelvis CT for 1/40 (2.5%), total bone scan for 1/40 (2.5%) and brain MRI for 1/40 (2.5%) patient.

117 clinical relapses (Fig. 3.8 and Table 3.6) were identified: 6/117 (5%) in the PB, 17/117 (14.5%) PLN, 51/117 (43.5%) PALN; 32/117 (27.5%) bone metastases, among them 17/32 osseous vertebrae, 5/32 pelvic bone lesions and 10/32 extra-axial; 27% patients (18/67) had progression with ≤ 3 identified metastases; 13.5% (9/67) had only 1 whereas 25.5% (17/67) had ≥ 4. 10.5% patients (7/67) had at least two anatomic sites of relapses, among under-, over-diaphragmatic nodes, bone or visceral lesions. 9%

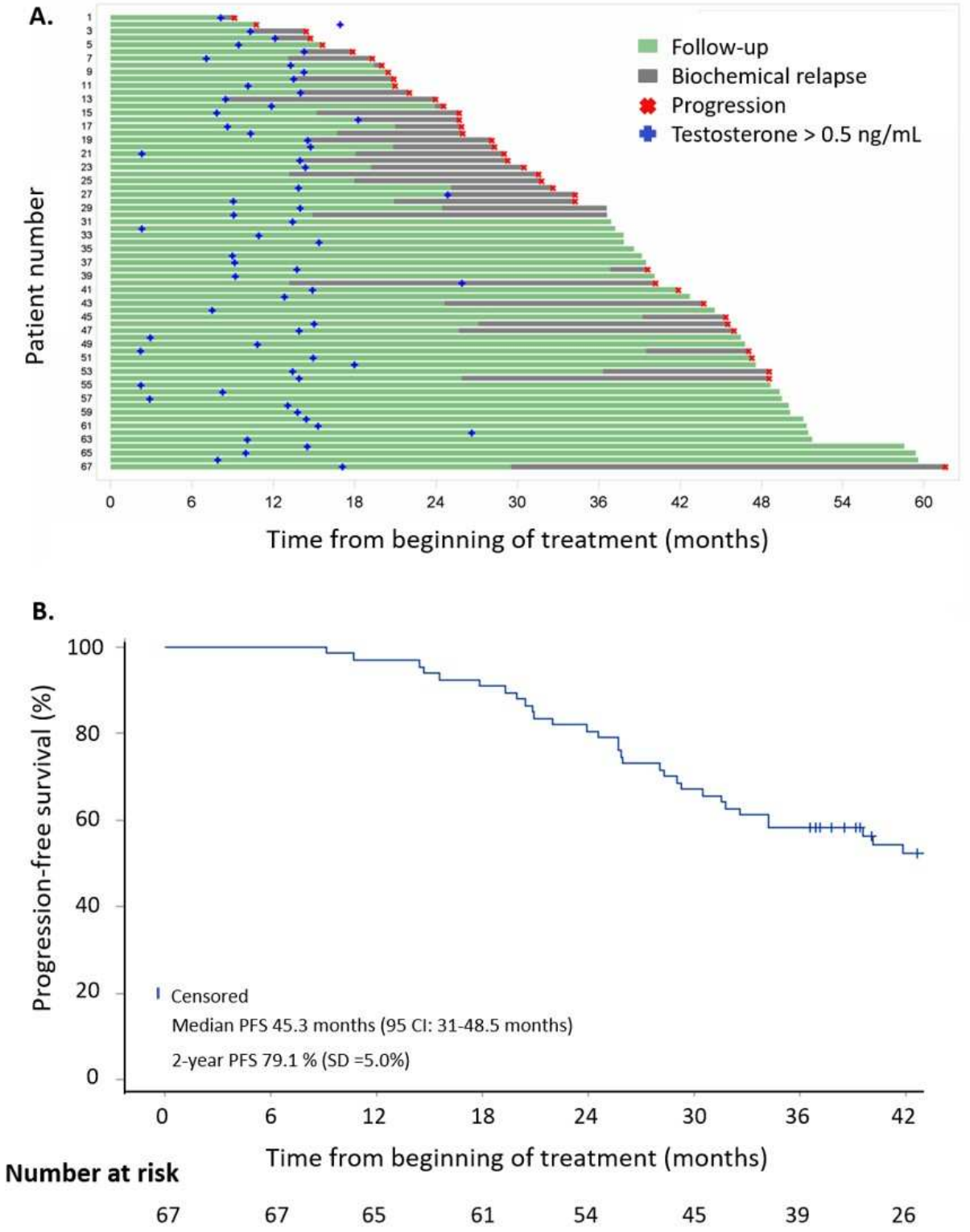

Figure 3.5: Panel A: Swimmer plot of individual patient PSA response. Each bar represents one subject in the study. Biochemical relapse: PSA > Nadir + 0.2 ng/mL (and > Nadir following prior prostate radiotherapy in case of conservative prostate treatment). Progression: PSA > PSA at inclusion and/or as per RECIST1.1 and/or death from any cause. Panel B: Progression-free survival.

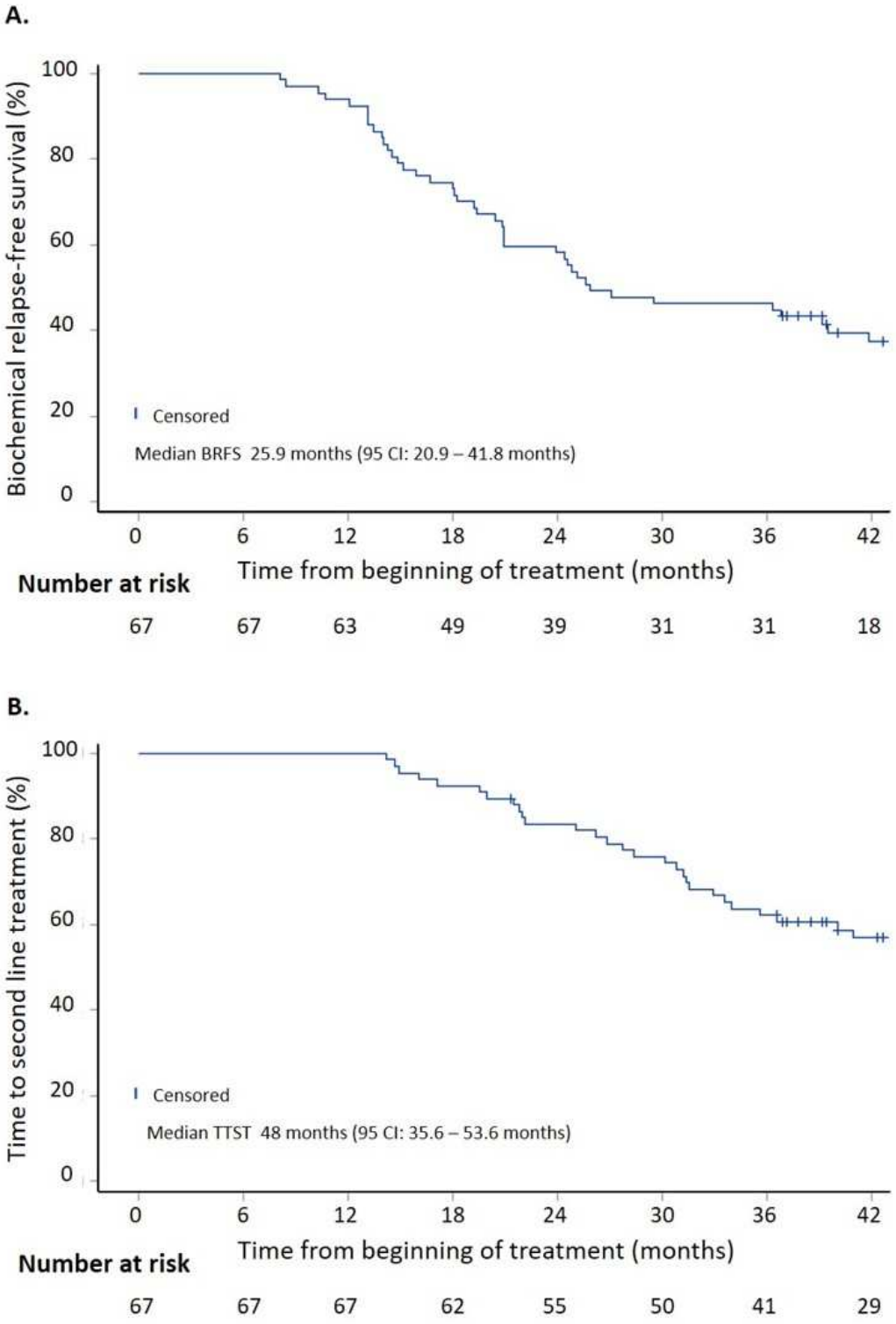

Figure 3.6: Panel A: Biochemical relapse-free survival. Panel B: Time to start a second line treatment.

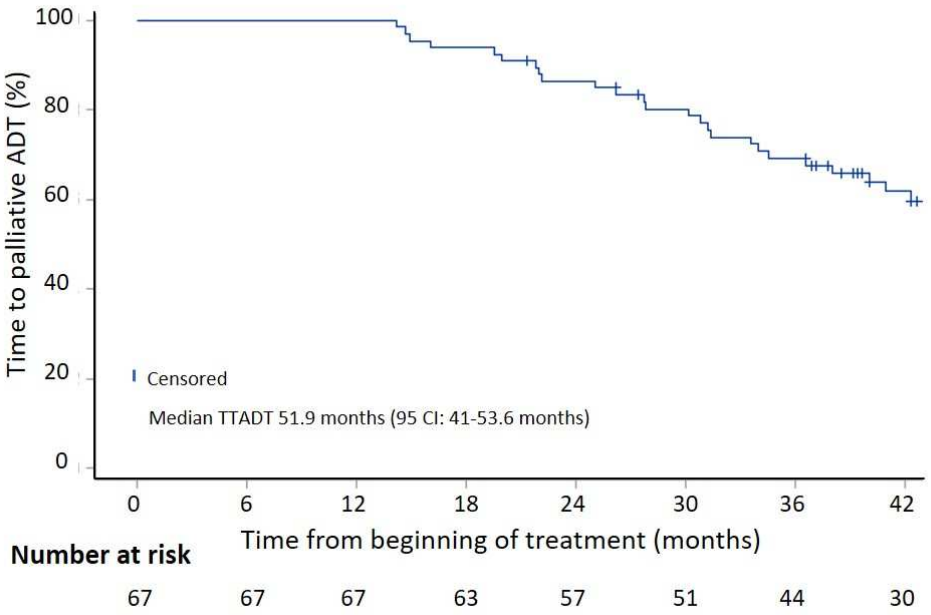

Figure 3.7: Time to start palliative androgen deprivation therapy (ADT).)

Table 3.5: Prognostic factors for progression-free survival in univariate analysis. EWPRT = high-dose whole pelvic radiotherapy; PSADT = PSA doubling time.

Parameter	p value	HR	95% HR CI
PSA at baseline*	0.2481	1.453	0.771-2.74
Gleason at diagnosis			
(> 7 vs ≤ 7)	0.6313	1.238	0.518-2.959
Time from diagnosis to EWPRT*	0.8095	1.081	0.575-2.032
Number of nodes			
(> 1 vs ≤ 1)	0.6712	0.867	0.45-1.673
PSADT			
(< 6 months vs ≥ 6 months)	0.8158	0.922	0.467-1.821
PSA at 6-month			
(< 0.5 vs ≥ 0.5 ng/mL)	<0.0001	8.453	3.367-21.219

*Dichotomized according to the median

Table 3.6: Distribution of metastases detected by PET at progression and minimal relapsing dose (DR_{min}^{EWPRT}) received within elective whole pelvis radiotherapy (EWPRT). The dose from prior prostatic or prostate bed radiotherapy was not considered below. Patients with metastases in separate anatomic regions were counted twice. PB = prostatic bed; PLN = pelvic lymph nodes; PALN = para-aortic lymph nodes.

(67 pts)	**Patients**		**Relapses**		**DR_{min}^{EWPRT} (Gy)**
	n	%	n	%	
Total	35	52%	117	100%	
PB	6	9%	6	5%	6.5 [1.5; 4; 65; 68.5]
PLN	10	15%	17	14.5%	15 [2; 4; 49; 54]
PALN	16	24%	51	43.5%	1.5 [0; 1; 2; 6]
Bone	12	18%	32	27.5%	-
Others†	6	9%	11	9.5%	-
Multiple‡	7	10.5%	-	-	-

†Neither under-diaphragmatic nor bone metastases
‡At least 2 distinct anatomical relapsing sites among under-, above-diaphragmatic nodes, bone, visceral

patients (6/67) had over-diaphragmatic lymph nodes, lung, liver or brain metastases.

The median minimal relapsing dose for the pelvis was DR_{min}= 15 Gy [range, 2-54 Gy]. 6/17 (35.5%) PLN recurrences were radioresistant (Table 3.7), every time for patients without prior prostatic bed radiotherapy except for one who had an ilio-obturator relapse with $DR_{min}$of 60 Gy from the prior PB-RT and 31 Gy from EWPRT. 11/17 (64.5%) recurrences were geographic-missed: 4/17 (23.5%) occurred in the common iliac vessels or aortoiliac bifurcation but outside the whole pelvis PTV whereas they should have been covered according to the protocol; the other 7/17 (41%) were inguinal, pre-vesical and peri-rectal nodes, thus outside both the radiation field junction with prior prostatic radiotherapy and the recommended pelvic limits.

Six patients (2 from Groups A and B; and 4 from Groups C and D) had PB local relapse, all radioresistant with $DR_{min} \geq$ 50 Gy. The median time for PB local relapses for patients with prior PB-RT was 121 months [range, 83-164].

Patients with prior PB-RT had worst CPFS compared to patients of Groups A and B (HR = 2.1, p 0.038) but in univariate analysis. The median time from prostate cancer diagnosis was larger for these patients (91 versus 53.5 months) but this factor was not significantly associated with CPFS (HR = 0.83, p 0.6). The median minimal dose (D98) delivered to the PTV for FCH-PET positive PLN and whole pelvis was comparable in both groups (Fig. 3.2 and Table 3.2), independently of prior prostate radiotherapy. The incidence of pelvic relapses was also comparable in the two groups (16% versus 14% for patients of group A+B and C+D, respectively).

Patients with total PLN CTV larger than 10 cm^3 had higher risk of under-diaphragmatic relapsesÂ (OR = 8.0 95% CI: 1.66-38.29). The proportion of under-diaphragmatic relapses was significantly increased in patients with common iliac or aorto-iliac bifurcation FCH-PET positive PLN (N=10/15,

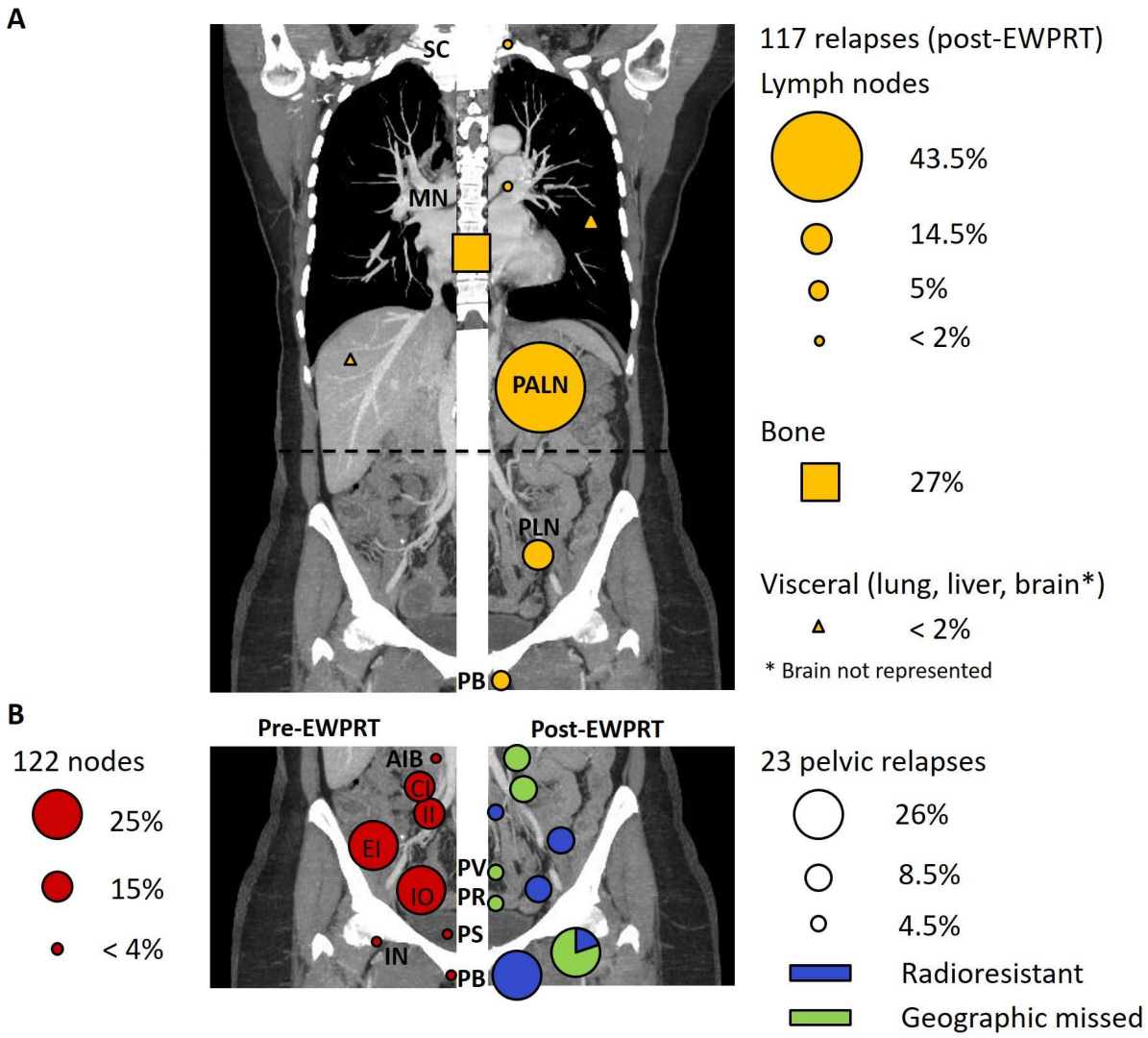

Figure 3.8: Panel A: Post-elective whole pelvis radiotherapy (EWPRT) distribution of relapses (yellow). SC = supraclavicular nodes; MN = mediastinal nodes; PALN = para-aortic lymph nodes; PLN = pelvic lymph nodes; AIB = aortoiliac bifurcation; CI = common iliac; II = internal iliac; EI = external iliac; IO = ilio-obturator; IN = inguinal; PS = pre-sacral; PV = peri-vesical; PR = para-rectal; PB = prostatic bed. Dashed line : upper limit of the whole pelvis radiation field from the protocol. Panel B: Pre-(red) and post-EWPRT distribution of pelvic radioresistant (blue) and geographic-missed (green) relapses. Pelvic relapses were considered as radioresistant (geographic-missed) in case of the minimal relapsing dose $DR_{min} \geq (<)$ 50 Gy with either EWPRT or prior prostate bed radiotherapy.

Table 3.7: Distribution of metastases at progression for patients of Groups A+B and C+D (prior prostate radiotherapy) and rate of pelvic radioresistant recurrences (minimal relapsing dose $DR_{min} \geq 50$ Gy with either elective whole pelvis or prior prostate radiotherapy). Patients with metastases in distinct anatomic sites were counted twice.
Others = neither under-diaphragmatic nodes nor bone metastases; Anatomic sites: PB = prostatic bed; PLN = pelvic lymph nodes; PALN = para-aortic lymph nodes; AIB = aortoiliac bifurcation; CI = common iliac; II = internal iliac; EI = external iliac; IO = ilio-obturator; IN = inguinal; PS = pre-sacral; PV = peri-vesical; PR = para-rectal.

	Groups A+B			**Groups C+D**		
Total	37			80		
	n	%	$DR_{min} \geq 50$ Gy	n	%	$DR_{min} \geq 50$ Gy
PLN	9	24.5%	5/9	8	10%	1/8[†]
AIB	1	2.5%	0/1	1	1.5%	0/1
CI	-	-	-	2	2.5%	0/2
II	1	1.5%	1/1	-	-	-
EI	2	5.5%	2/2	-	-	-
IO	1	2.5%	1/1	1	1.5%	1/1[†]
IN	3	8%	1/3	3	4%	0/3
PR	-	-	-	1	1.5%	0/1
PV	1	2.5%	0/1	-	-	-
PB	2	5.5%	2/2	4	5%	4/4[†]
PALN	17	46%	-	34	42.5%	-
Bone	4	11%	-	28	35%	-
Others	5	13.5%	-	6	7.5%	-

[†] $DR_{min} \geq 50$ Gy from prior prostatic bed radiotherapy

Table 3.8: Treatment at progression following high-dose elective whole pelvis radiotherapy for patients of Groups A+B and C+D (with prior prostatic radiotherapy). ADT = androgen deprivation therapy; SBRT = stereotactic radiotherapy; RT = radiotherapy.

	Patients	ADT	SBRT	SBRT+ADT	RT+ADT	Surveillance	Other*
Total	40	21 (52.5%)	9 (22.5%)	4 (10%)	2 (5%)	2 (5%)	2 (5%)
A+B	12	6 (50%)	3 (25%)	2 (16.5%)	-	-	1 (8.5%)
C+D	28	15 (53.5%)	6 (21.5%)[†]	2 (7%)	2 (7%)	2 (7%)[‡]	1 (3.5%)

*Inguinal lymphadenectomy and lung segmentectomy
[†]SBRT + antiPDL1 (Durvalumab) for 1 patient
[‡]Prostate apical relapse following brachytherapy for 1 patient

p=66.5% vs N=15/52, p=29% in the other patients) (p = 0.007). Neither PSA at baseline, nor Gleason at diagnosis nor PSADT nor number of PLN nor total PLN GTV ($\leq$ 4 cm^3) were significantly associated with under-diaphragmatic (PB, PLN or PALN) relapses.

3.6 Treatment at progression

Almost half of progressive patients have been treated either by ADT (52.5%, 21/40) or new course of radiotherapy (37.5%, 15/40). In the latter case, SBRT with or without short-term ADT was favored (Table 3.8). An example is shown in Fig. 3.9. Among the 5 patients without identified metastases at progression, only 1 is still ADT-free at 50 months from EWPRT.

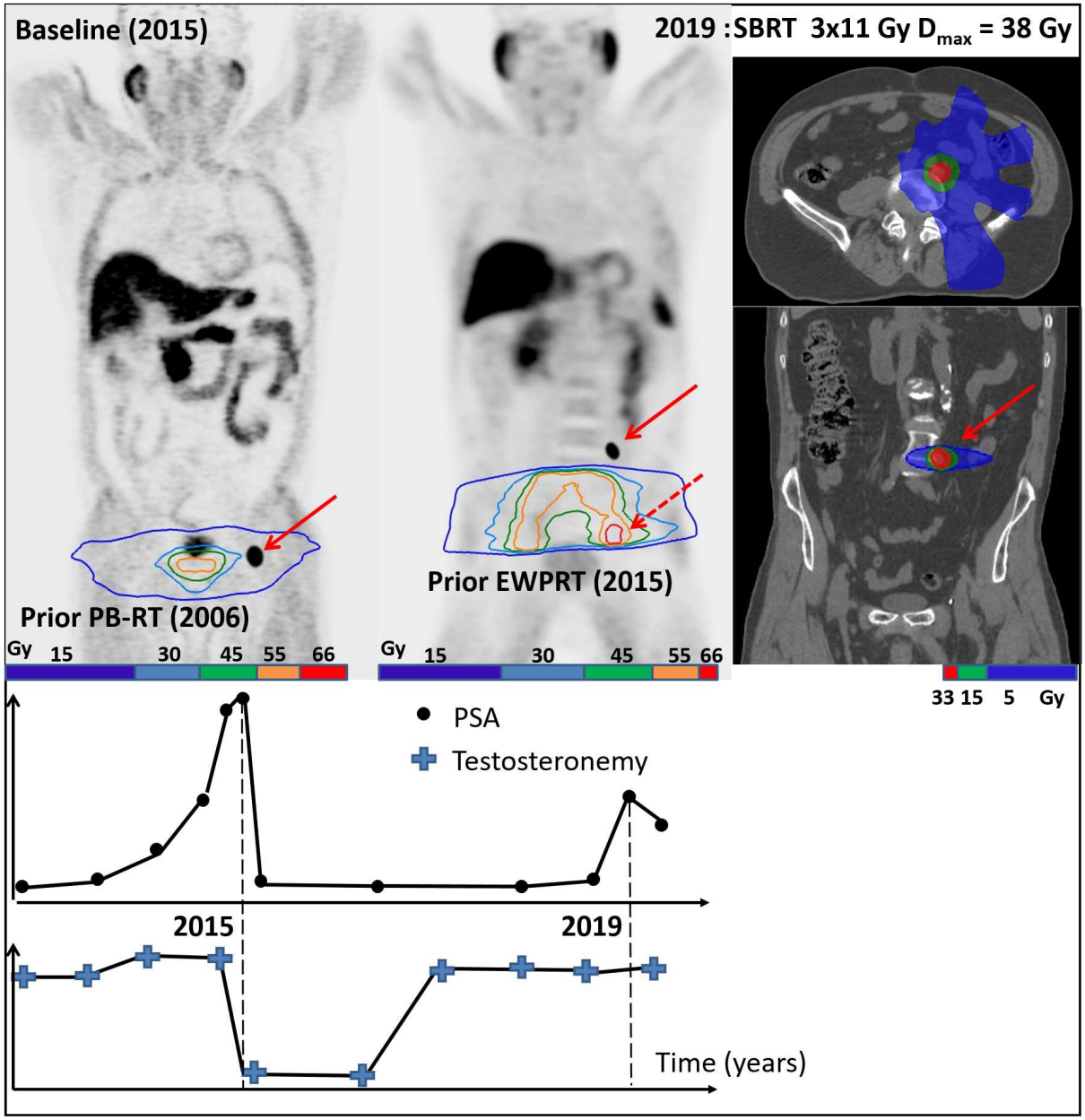

Figure 3.9: Example of a patient treated by prior prostatic bed radiotherapy (PB-RT) in 2006 (biochemical relapse following radical prostatectomy) and then by high-dose elective whole-pelvis radiotherapy (EWPRT) for one FCH-PET-positive lymph node into the left external iliac vessels (red arrow) in 2015, and then who had in 2019 after years of tumor control, one new FCH-PET positive left peri-aortic node (red arrow) while PET negative pelvic nodes (red dashed arrow). Such new oligorecurrent relapse was treated by three fractions of stereotactic radiotherapy (SBRT) in 2019.

Chapter 4

Discussion

This trial addressed the use of 6-month ADT combined with salvage high-dose pelvic radiotherapy in prostate cancer patients whose oligometastatic relapse has been identified on FCH-PET imaging. Our findings provide evidence of a prolonged progression-free survival in these patients at the cost of a limited toxicity even in those with a past history of prostate bed radiotherapy. To our knowledge, this trial is the first to prospectively address the efficacy and toxicity of such elective pelvic radiotherapy combined with short-term ADT.

In the metastatic setting, ADT is the standard of care and can be administered continuously or intermittently [Cornford *et al.* (2017)]. In patients for whom metastases were diagnosed using conventional imaging (CT and/or total bone scan), a study was not able to rule out a 20% greater risk of death with intermittent than with continuous therapy [Hussain *et al.* (2013)]. In patients with a rising PSA and no visible metastases on conventional imaging, intermittent ADT was also non-inferior to continuous therapy [Crook *et al.* (2012)]. In our situation where conventional imaging was not able to detect metastatic lymph nodes, intermittent ADT can be considered as a validated option.

In the study of Crook *et al*, ADT was given for 8 months and progression was defined as PSA levels higher than 10 ng/mL or clinical progression [Crook *et al.* (2012)]. Within this definition, the median time to progression was 28.1 months. In our study, we have chosen a 6-month ADT duration as already proposed by randomized trials in localized [Jones *et al.* (2011), D'Amico *et al.* (2008)] or biochemically-relapsing prostate cancer [Carrie *et al.* (2019)]. Progression in our study was mainly assessed by FCH-PET imaging and at a median PSA level of around 4 (IQR: 2.4-4.9) ng/mL, thus lower than the 10 ng/mL cut off from the study of Crook *et al* [Crook *et al.* (2012)]. However, we found a 40.1 months median PFS in our study and a 51.9 months median TTADT. Salvage high-dose pelvic radiotherapy added to 6-month ADT may thus i) increase PFS ii) while delaying the need for palliative ADT. Of note, 45% patients achieved a persisting biochemical complete response at 3 years, while achieving normal testosterone levels. Longer follow-up is needed to assess if such strategy can even cure some patients. We could not determine predictive factors of progression following salvage EWPRT such as number of lymph nodes or tumor characteristics, since a vast proportion of patients had only one oligorecurrent PLN and a long PSA doubling-time. Predictive factors will be evaluated in a large ongoing randomized trial (Oligopelvis 2 GETUG P12, NCT03630666) comparing intermittent ADT with or without salvage EWPRT.

Importantly, tumor control was achieved at the cost of a limited toxicity [Vaugier *et al.* (2019)]. Despite high doses to lymph nodes close to the intestine or the bladder, grade 3 toxicity was infrequent,

corroborating previous studies for salvage elective [Schick *et al.* (2013), Picchio *et al.* (2014), Fodor *et al.* (2017), Tran *et al.* (2018), Ingrosso *et al.* (2020), Sato *et al.* (2020)] or dose-escalating prophylactic [Bayley *et al.* (2010), Adkison *et al.* (2012), Reis Ferreira *et al.* (2017)] pelvis radiation. Salvage pelvic radiotherapy was administered in a large proportion of patients with a previous history of prostate or prostate bed irradiation. Overlapping fields partially irradiated again pelvic tissues and this may have increased toxicity. Despite that, we did not observe increased toxicity between patient with a past history of prostate radiotherapy or not. Similar tolerance profile was noted in pelvic reirradiation using SBRT [Jereczek-Fossa *et al.* (2012), Decaestecker *et al.* (2014), Jereczek-Fossa *et al.* (2019), D'Agostino *et al.* (2019), Pasquier *et al.* (2019)]. Further study regarding the repair mechanisms of radioinduced pelvic injury is highly recommended.

Metastasis-directed therapy (MDT) using radiotherapy is an active area of research whose positive impact on overall survival was demonstrated in various primitive histologies [Palma *et al.* (2020)]. In pelvic nodal oligorecurrent prostate cancer specifically, radiotherapy can be administered either to the whole pelvis as proposed in our study; or to the involved lymph nodes using SBRT. ADT can be combined with both treatments. SBRT versus observation was shown to increase the progression-free survival and delay the need for ADT in prospective randomized trials [Ost *et al.* (2018), Phillips *et al.* (2020)] or in prospective/retrospective analyses [Ost *et al.* (2016a), Siva *et al.* (2018), Deek *et al.* (2020)] with median distant progression-free survivals, TTNI and TTADT around 20-28 months. In comparison in our study, median CPFS, TTNI and TTADT were around 47-52 months, suggesting that EWPRT could be superior to SBRT. This was already suspected from retrospective studies [De Bleser *et al.* (2019), Lépinoy *et al.* (2019)]. Salvage lymphadenectomy has also been proposed for PLN oligorecurrences at the cost of a limited toxicity [Suardi *et al.* (2015), Ploussard *et al.* (2019)]. A pooled analysis of multiple series showed that complete biochemical response rates ranged from 13.0% to 79.5% (mean 44%). The 2-year biochemical relapse-free survival rates ranged from 23% to 64% [Ploussard *et al.* (2019)], yielding comparable results to our study. Whether high-dose pelvic radiotherapy compares favorably to extended lymphadenectomy or whether both treatments need to be added remain open questions. An international randomized phase II trial (PEACE 5-STORM, NCT03569241) is currently comparing 6-month ADT and SBRT or lymphadenectomy with or without whole pelvis prophylactic radiotherapy.

In our study, 60% of clinical relapses were under-diaphragmatic nodes; one third were bone metastases. Similar number of patients (around 30%) had either oligo- ($\leq$ 3 new metastases) or diffuse progression (> 4). Such pattern of relapse highlights that further progression of pelvic nodal oligorecurrent prostate cancer remained nodal at first and oligorecurrent for one in two progressive patients. Similar results were found in the retrospective analyses employing ^{68}Ga-PSMA-PET guided EWPRT [Soldatov *et al.* (2019)] or SBRT [Ost *et al.* (2016b), Deek *et al.* (2020)].

Importantly, pelvic recurrences in our cohort were limited (< 15%). In comparison, most patients treated by nodal SBRT had further relapse in the pelvic area [Ost *et al.* (2016b), Deek *et al.* (2020)]. The risk of missing microscopic disease in neighboring nodes with SBRT is counterbalanced by the possibility of repeating SBRT [Jereczek-Fossa *et al.* (2012), Decaestecker *et al.* (2014)]. In our cohort, almost half of patients with progression were treated by a new course of radiotherapy, SBRT at first. Interestingly, around 5% patients had further late PB local relapse with median time around 10 years from PB-RT, corroborating the risk of late prostatic bed relapse as already reported [Jereczek-Fossa *et al.* (2019), D'Agostino *et al.* (2019), Pasquier *et al.* (2019), Créhange *et al.* (2014)]. The feasibility of SBRT prostatic bed reirradiation is currently investigated in a phase I trial (REPAIR-GETUG P16, NCT04536805). For FCH-PET positive pelvic oligorecurrences, all these observations enhance the rationale of i) considering nodal radia-

tion treatment combined with short-term ADT; ii) employing EWRT at first rather than SBRT for tackling potential pelvic micrometastases in the same time and iii) considering SBRT in case of a further oligoprogression.

The pattern of nodal relapses in our study could have strong clinical consequences for EWRT of patients with pelvic oligorecurrences. The recommendations for prophylactic pelvis radiotherapy commonly advise to cover the nodal regions with an estimated risk of involvement > 5% but the limits of the radiation fields i) are still controversial in practice without clear consensus among the RTOG, UK CRUK PIVOTAL and GETUG groups [Lawton *et al.* (2009), Harris *et al.* (2015), Sargos *et al.* (2015)], and ii) may depend on the history of prostate cancer (high-risk localized versus recurrent cancer). The risk of missing nodal micrometastases above or outside the radiation field limits was already pointed out, e.g. in the treatment of localized or locally advanced prostate cancer [Spratt *et al.* (2017), De Bruycker *et al.* (2019), Liskamp *et al.* (2020)]. A recent study based on personalized sentinel pelvic lymph nodes has shown that around 20% of pathologic nodes were missed with the current standard guidelines of pelvic radiotherapy, mostly at the common iliac level [Michaud *et al.* (2020)]. Recently, an update of the 2009 RTOG consensus guidelines has revealed the regions presenting the greatest variability of treatment, mainly the proximal common iliac vessels, the transition between external iliac and inguinal vessels and the peri-rectal spaces [Hall *et al.* (2020)]. In our study, we have chosen the aortoiliac bifurcation as the upper limit of the pelvic radiation fields, in coherence with the GETUG and the recently updated RTOG recommendations [Sargos *et al.* (2015), Hall *et al.* (2020)]. Pelvic recurrences were i) rare and ii) half radioresistant half geographic-missed when excluding the patients with a major deviation to the delineation protocol. These observations together with the absence of notable toxicity, confirm the role for both the high-dose and the radiation field limits for EWPRT as considered in our study.

By contrast, almost half of the clinical relapses occurred in the peri-aortic vessels thus above the standard pelvic limit, and under-diaphragmatic relapses were mostly geographic-missed. The presence of peri-aortic nodal metastases in case of biochemical relapse was already noted with rates of FCH-PET positive PALN yielding until 20% [Lépinoy *et al.* (2014), Parker *et al.* (2017)]. Considering extended prophylactic radiation fields could be interesting in this regard, e.g. to deal with potential individual variations in lymphatic drainage (e.g. peri-rectal or inguinal) [Michaud *et al.* (2020)] or microscopic peri-aortic invasion [Sargos *et al.* (2015), Jethwa *et al.* (2019)]. The toxicity of prophylactic peri-aortic radiation for example - although feasible [Jouglar *et al.* (2016)] - however prohibits using it systematically for all patients [Morris(2015), Nicholas *et al.* (2017)]. PET imaging with more sensitive tracers such as PSMA could be relevant for the identification of the appropriate candidates [Bluemel *et al.* (2016), van Leeuwen *et al.* (2016),Calais *et al.* (2018)]. Coupled with specific antibodies or radioactive elements, these tracers could even play an important role in therapeutics as first-line or consolidative treatment [Evans-Axelsson *et al.* (2016), Chakravarty *et al.* (2018), Sathekge *et al.* (2019)]. Whether FCH-PET positive PLN in common iliac vessels or large pelvic tumor charge might be associated with higher risk of under-diaphragmatic relapses and thus benefit of an extended and/or para-aortic EWRT, is an open question which requires larger cohort to be answered.

This trial has several limitations: the limited number of patients and the absence of randomization inherent with the trial design firstly. Secondly, FCH was the only radiotracer available at the time of initiation of the study. Now PSMA PET tracers are more largely available and may select patients with a more precise definition of the extension of the disease at biochemical relapse.

Chapter 5

Conclusions

Combined high-dose pelvic salvage radiotherapy and 6-month ADT in pelvic nodal oligorecurrences of prostate cancer allowed for i) prolonged tumor control; ii) long second treatment- or ADT-free intervals; iii) at a cost of a limited toxicity, even in the patients with a past history of prostatic irradiation. Around 45% patients were in complete remission three years after the procedure. Further relapses were revealed by PET for 80% patients with progression. Pelvic recurrences (<15%) were limited. Half of relapses were nodes in the para-aortic vessels thus above the radiation field limits, and one third were bone metastases. This suggests that further progression of pelvic nodal oligorecurrent prostate cancer may remain a nodal disease at first and justifies the role for nodal irradiation. PET radiotracers with higher sensibility and/or extended prophylactic radiation up to the para-aortic vessels but for appropriate candidates, would be relevant in this regard. Importantly, around 30% patients were still oligometastatic at further progression with further metastases-directed therapies as options for the prolongation of ADT-free intervals.

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NOM : VAUGIER PRENOM : Loïg

Titre de Thèse : Etude OLIGOPELVIS: Place de la radiohormonothérapie pelvienne de rattrapage en situation de récidive oligométastatique ganglionnaire de cancer prostatique hormononaif

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RESUME

RATIONNEL

Le cancer de prostate au stade oligométastatique est un défi pour les traitements de rattrapage locorégionaux. L'hormonothérapie par castration chimique (ADT) est le standard en situation métastatique mais la radiothérapie peut en différer le recours de façon prolongée dans le cas de rechutes ganglionnaires pelviennes isolées.

MÉTHODES

Nous avons réalisé un essai ouvert de phase II combinant radiothérapie modulée en intensité á forte dose et ADT courte (6 mois) dans le cas d'oligorécidives ($\leq$ 5) ganglionnaires pelviennes détectées par TEP Fluorocholine. La dose prescrite était de 54 Gy en fractions de 1,8 Gy jusqu'á 66 Gy en fractions de 2,2 Gy sur les ganglions pathologiques. Le critère d'évaluation principal était le taux de survie sans progression (PFS) à 2 ans; la progression était définie par: deux valeurs de PSA au-dessus du PSA à l'inclusion et/ou progression selon RECIST 1.1 et/ou décès toute cause confondue.

RÉSULTATS

Entre août 2014 et juillet 2016, 67 patients ont été inclus dans 15 centres. Environ la moitié d'entre eux avaient déjà reçu un traitement de radiothérapie prostatique. L'âge médian était de 67,7 ans. Après un suivi médian de 37,8 mois, la PFS à 2 ans était de 79,1%. La PFS médiane était de 45,3 mois. A 3 ans, 44,8% des patients étaint en réponse biochimique complète. Les grade 2+ de toxicité génito-urinaire et gastro-intestinale à 2 ans étaient respectivement de 10% et 6%. Les patients avec irradiation prostatique antérieure n'ont pas présenté de toxicité accrue. Environ la moitié des rechutes cliniques étaient des rechutes ganglionnaires lomboaortiques, un tiers des métastases osseuses. Le taux de récidive pelvienne (14,5%) était faible. 27% des patients ont eu $\leq$ 3 métastases détectées à progression. ADT et radiothérapie stéréotaxique ont été effectuées chez 52,5% et 32,5% des patients respectivement.

INTERPRETATION

La radiothérapie pelvienne de rattrapage à forte dose couplée à 6 mois d'hormonothérapie a permis d'obtenir un contrôle tumoral prolongé dans le cas de rechutes oligométastatiques ganglionnaires pelviennes de cancer de prostate, et ce avec une très faible toxicité, y compris chez les patients avec antécédent de radiothérapie prostatique. Environ 45% des patients étaient en réponse biochimique complète à 3 ans, tandis que 30% étaient á nouveau oligométastatiques avec possibilité de second traitement de rattrapage par radiothérapie.

MOTS-CLEFS

radiothérapie pelvienne; cancer de prostate oligométastatique; IMRT guidée par TEP