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Platinum Priority – Prostate Cancer
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OLIGOPELVIS GETUG P07, a Multicenter Phase II Trial of Combined High-dose Salvage Radiotherapy and Hormone Therapy in Oligorecurrent Pelvic Node Relapses in Prostate Cancer

Stéphane Supiot [a,b,*], ***Loig Vaugier*** [a], ***David Pasquier*** [c,d], ***Xavier Buthaud*** [e], ***Nicolas Magné*** [f], ***Didier Peiffert*** [g], ***Paul Sargos*** [h], ***Gilles Crehange*** [i], ***Pascal Pommier*** [j], ***Genevieve Loos*** [k], ***Ali Hasbini*** [l], ***Igor Latorzeff*** [m], ***Marlon Silva*** [n], ***Fabrice Denis*** [o], ***Jean-Léon Lagrange*** [p], ***Cyrille Morvan*** [q], ***Loic Campion*** [r], ***Audrey Blanc-Lapierre*** [r]

[a] *Department of Radiation Oncology, Institut de Cancérologie de l'Ouest, Nantes, St-Herblain, France;* [b] *Centre de Recherche en Cancérologie Nantes-Angers (CRCNA), UMR 1232 Inserm – 6299 CNRS, Institut de Recherche en Santé de l'Université de Nantes, Nantes Cedex, France;* [c] *Academic Radiation Oncology Department, Centre Oscar Lambret, Lille, France;* [d] *Centre de Recherche en Informatique, Signal et Automatique de Lille, CRIStAL UMR CNRS 9189, Université de Lille, Lille, France;* [e] *Department of Radiation Oncology, Centre Catherine de Sienne, Nantes, France;* [f] *Department of Radiation Oncology, Institut de Cancérologie de la Loire, St Priest en Jarez, France;* [g] *Department of Radiation Oncology, Centre Alexis Vautrin, Vandoeuvre-lès-Nancy, France;* [h] *Department of Radiation Oncology, Institut Bergonié, Bordeaux, France;* [i] *Department of Radiation Oncology, Georges-Francois Leclerc Cancer Center, Dijon, France;* [j] *Department of Radiation Oncology, Centre Léon Bérard, Lyon, France;* [k] *Department of Radiation Oncology, Centre Jean Perrin, Clermont-Ferrand, France;* [l] *Department of Radiation Oncology, Clinique Pasteur, Brest, France;* [m] *Department of Radiation Oncology, Oncorad Clinique Pasteur, Toulouse, France;* [n] *Department of Radiation Oncology, Centre Francois Baclesse, Caen, France;* [o] *Department of Radiation Oncology, Centre Jean Bernard, Le Mans, France;* [p] *Department of Radiation Oncology, Hopital Henri Mondor, Créteil, France;* [q] *Department of Nuclear medicine, Institut de Cancérologie de l'Ouest, Boulevard J. Monod, Nantes, St-Herblain, France;* [r] *Department of Biostatistics, Institut de Cancérologie de l'Ouest, Boulevard J. Monod, Nantes, St-Herblain, France*

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Abstract

Background: Oligorecurrent pelvic nodal relapse in prostatic cancer is a challenge for regional salvage treatments. Androgen depriving therapies (ADTs) are a mainstay in metastatic prostate cancer, and salvage pelvic radiotherapy may offer long ADT-free intervals for patients harboring regional nodal relapses.
Objective: To assess the efficacy of the combination of ADT and salvage radiotherapy in men with oligorecurrent pelvic node relapses of prostate cancer.
Design, setting, and participants: We performed an open-label, phase II trial of combined high-dose intensity-modulated radiotherapy and ADT (6 mo) in oligorecurrent (five or fewer) pelvic node relapses in prostate cancer, detected by fluorocholine positron-emission tomography computed tomography imaging.
Outcome measurements and statistical analysis: The primary endpoint was 2-yr progression-free survival defined as two consecutive prostate-specific antigen levels above the level at inclusion and/or clinical evidence of progression as per RECIST 1.1 and/or death from any cause.
Results and limitations: Between August 2014 and July 2016, 67 patients were recruited in 15 centers. Half of the patients had received prior prostatic irradiation. The median age was 67.7 yr. After a median follow-up of 49.4 mo, 2- and 3-yr progression-free

* Corresponding author. Department of Radiation Oncology, Institut de Cancérologie de lOuest, Boulevard J. Monod, F-44800 Nantes, St-Herblain, France. Tel. +33 240679913; Fax: +33 240679722.
E-mail address: stephane.supiot@ico-unicancer.fr (S. Supiot).

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Pelvic radiotherapy
Intensity-modulated radiotherapy
Prostate bed irradiation
Lymphadenectomy
Positron-emission tomography
prostate-specific membrane antigen
Choline
Fluciclovine
Stereotactic body radiotherapy
Stereotactic ablative radiotherapy
Stereotactic radiotherapy

survival rates were 81% and 58%, respectively. Median progression-free survival was 45.3 mo. The median biochemical relapse–free survival (BRFS) was 25.9 mo. At 2 and 3 yr, the BRFS rates were 58% and 46%, respectively. Grade 2 + 2-yr genito-urinary and gastrointestinal toxicities were 10% and 2%, respectively.

Conclusions: Combined high-dose salvage pelvic radiotherapy and ADT appeared to prolong tumor control in oligorecurrent pelvic node relapses in prostate cancer with limited toxicity. After 3 yr, nearly half of patients were in complete remission. Our study showed initial evidence of benefit, but a randomized trial is required to confirm this result.

Patient summary: In this report, we looked at the outcomes of combined high-dose salvage pelvic radiotherapy and 6-mo-long hormone therapy in oligorecurrent pelvic nodal relapse in prostatic cancer. We found that 46% of patients presenting with oligorecurrent pelvic node relapses in prostate cancer were in complete remission after 3 yr following combined treatment at the cost of limited toxicity.

1. Introduction

The major cause of death among prostate cancer patients is the development of metastases. The natural history of the metastatic process has been revealed by recent imaging techniques based on nonspecific prostate cancer markers such as fluorocholine (FCH), prostate-specific membrane antigen (PSMA), or fluciclovine positron-emission tomography (PET) [1–3]. These have made it possible to identify limited metastatic relapses in prostatic cancer, especially in small pelvic lymph nodes (PLNs), which occur early and at low prostate-specific antigen (PSA) levels, when conventional imaging is unable to reveal disease localization due to the small size (frequently <10 mm) [1,4]. This oligometastatic state may be an apparent turning point between still-controllable regional disease that might be managed with local intervention, and diffuse disease for which androgen depriving therapies (ADTs) are the mainstay [5,6]. Oligorecurrent prostate cancer is now the preferred term for designating such relapses after primary curative-intent treatments [7].

In locally advanced disease, the role of radiotherapy in the management of micrometastatic lymph nodes is highly debated [8,9]. In the salvage postprostatectomy setting, there is a further lack of clear evidence regarding the role of radiotherapy in lymph nodes [10]. Metastasis-directed therapy, mostly using stereotactic radiotherapy to PLNs is one option, and it has been shown to decrease biochemical relapse and delay the need for ADT [6,11]. However, most patients relapse in the pelvic area [12,13]. Salvage elective node radiotherapy (ENRT) with an additional boost to any PET-positive PLN is another attractive option, but has the advantage of tackling the potential pelvic micrometastatic invasion. The best current evidence available for ENRT is derived from retrospective studies with varying doses and schedules of radiotherapy [14–18].

The main objective of this phase II trial was to assess the efficacy of high-dose salvage ENRT in a prospective manner in a well-defined population. We hypothesized that such ENRT combined with 6-mo of ADT would achieve a 2-yr progression-free survival rate of 70%. Here, we present the main objective of the trial after a minimum follow-up of 3 yr.

2. Patients and methods

2.1. Study design and participants

The complete trial design has been published previously [19]. Pelvic (below the aortic bifurcation) oligorecurrent castration-sensitive prostate cancer patients with fewer than six metastatic PLNs detected using FCH-PET were included in the trial. FCH-PET/computed tomography (CT) images were scored as positive when focal tracer accumulation was greater than background activity or tracer physiological distribution. The diagnosis of malignant lymph nodes following a PET analysis was based on visual assessment of increased focal FCH uptake corresponding to lymph nodes on the CT image, even if they were <10 mm as described by Colombie et al [1]. Images at relapse were centrally reviewed blindly by a nuclear oncologist (C.M.). If dubious prostate or prostate bed FCH uptake was noted, pelvic magnetic resonance imaging was performed to assess for local relapse. If ADT had been administered previously to the patient, a minimum of 6-mo wash-out period was required, and serum testosterone had to be >6 nmol/l prior to inclusion. Previous irradiation of the prostate or the prostate bed was allowed, provided that there was a minimum of 1 cm gap between the prostate and salvage pelvic radiotherapy fields. Patients with extrapelvic metastases or patients under active ADT were excluded from the trial.

The trial population was divided into four groups, each with a different treatment plan: (1) group A: previous radical prostatectomy and no previous prostate bed radiation, with fewer than six FCH-PET–positive PLNs; (2) group B: the same as group A, but with an FCH-PET–positive signal in the prostate bed, suggesting local relapse; (3) group C: both previous radical prostatectomy and salvage prostate bed radiation therapy; and (4) group D: previous irradiation of the prostate (brachytherapy or external beam radiotherapy).

2.2. Procedures

Image-guided intensity-modulated radiation therapy 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 pathological PLNs. Patients who had not received previous irradiation received 66 Gy in 2 Gy fractions to the prostatic bed, with up to 72 Gy in 2 Gy fractions in the case of prostatic bed local relapse. PLNs were contoured according to the recommendations in the RTOG consensus statement [20] modified by the GETUG group [21], including the common iliac, external iliac, internal iliac, presacral (S1-S3), and obturator regions. The upper limit was defined by the bifurcation of the abdominal aorta. Androgen blockade was achieved by luteinizing hormone releasing hormone agonist or antagonist injections for 6 mo, ideally administered either on

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the 1 st day of radiation therapy or in the 3 mo before the 1 st day of radiation therapy.

2.3. Outcomes

The primary objective of this study was to describe the 2-yr progression-free survival (PFS) rate in men with oligorecurrent pelvic node relapses of prostate cancer, receiving the combination of ADT with salvage radiotherapy. 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 or death from any cause.

Secondary objectives included biochemical relapse–free survival (BRFS), overall survival (OS), time to the start of a second-line treatment (TTST), time to start palliative ADT (TTADT), acute and late toxicity, and quality of life assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and PR25 questionnaires. Biochemical relapse was defined as two consecutive PSA levels of >0.2 ng/ml following the post-treatment nadir. For patients with prior organ-preserving prostate treatment (external beam radiotherapy or brachytherapy), biochemical relapse was defined as (1) a PSA level of >0.2 ng/ml following the post-treatment nadir and (2) a PSA level of more than the nadir following the prior organ-preserving prostate treatment. Toxicity (CTC-AE v4) and quality of life were evaluated prior to treatment and 1 mo after the completion of radiotherapy, and then every 6 mo for 2 yr. 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 mo after completion, every 6 mo for 2 yr, and then yearly until progression. Quality of life was evaluated prior to treatment and 1 mo the after completion of radiotherapy, and then every 6 mo for 2 yr using the EORTC QLQ C30 and PR25 questionnaires. PSA and testosterone levels were determined prior to radiotherapy, 1 mo after completion, and then every 6 mo. Repeat FCH-PET was performed at biochemical recurrence.

2.4. Statistical analysis

Patients with oligorecurrent pelvic node relapses detected by FCH-PET represent an intermediate group between patients with rising PSA alone and frank metastatic disease. To calculate the patient population, we relied on both studies relating to a rising PSA patient population [22] and first-line metastatic patients [23] observing 2-yr PFS rates of ≤50%. We therefore estimated that a BRFS rate at 2 yr of 70% would be a significant result. The one-step phase 2 Fleming design was applied. Based on the hypothesis of a 2-yr PFS rate of 70% with salvage PLN IG-IMRT combined with 6-mo ADT, 63 evaluable patients were required to demonstrate with a power of 95% and a one-sided alpha risk of 5% that the 2-yr PFS rate was >50% [19]. A target sample size of N = 70 was thus calculated to account for a 10% dropout rate.

Data from all evaluable patients were analyzed. PFS, BRFS, TTST, TTADT, and OS were computed from the beginning of treatment. Patients without the outcome were censored on the date of the last time the patient was known to be free of this outcome. The Kaplan-Meier method was applied to estimate survival curves [24]. We used Cox regression, assuming proportional hazards, to run post hoc exploratory univariate analyses to investigate the prognostic value of PSA levels at baseline on PFS, Gleason score at diagnosis, number of nodes, PSA level 6 mo after treatment initiation, PSA doubling time, and the time from initial treatment to the initiation of the treatment being studied. We estimated

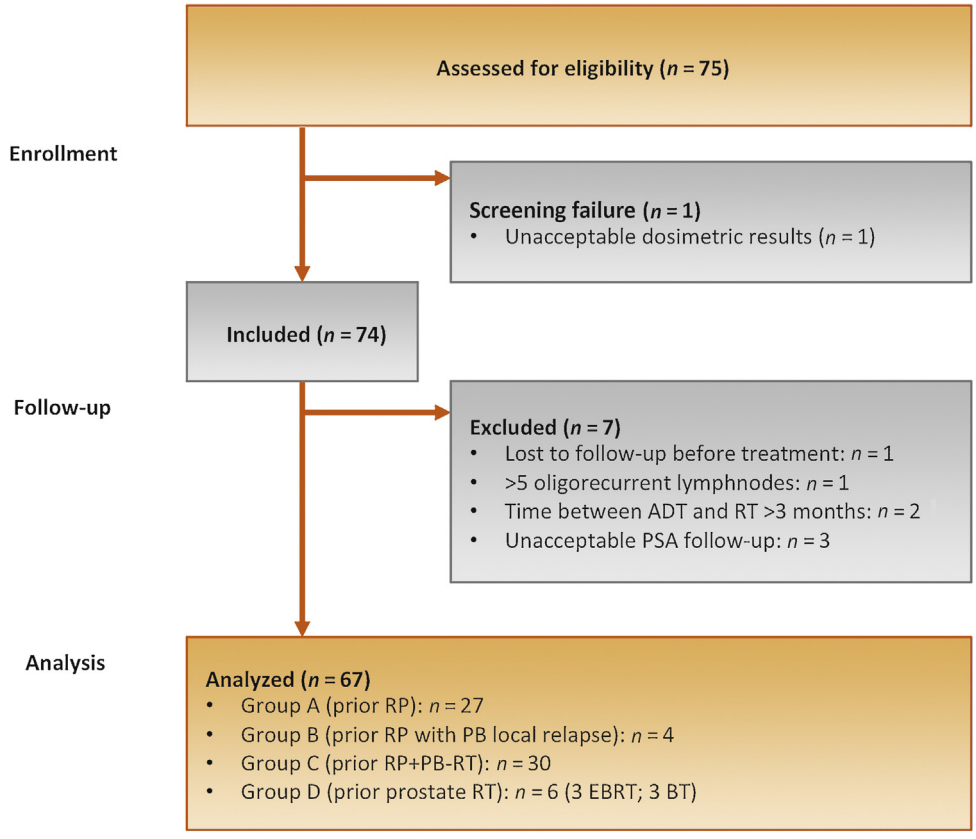

Fig. 1 – Flow chart of the trial. ADT = androgen depriving therapy; BT = brachytherapy; EBRT = external beam radiotherapy; PB = prostate bed; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy.

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hazard ratios (HRs) and their 95% confidence intervals (CIs). We did not impute missing data for covariates.

Quality of life scores at 18 and 24 mo were compared with baseline scores using a Wilcoxon signed test for matched pairs. All *p* values were corrected according to a Benjamini-Hochberg procedure to control for false discovery rates. Quality of life differences were considered clinically relevant when the value was >10.

All *p* values were based on two-sided tests and were considered significant if <0.05. We used SAS version 9.4 for the analyses.

This trial has been registered under number NCT02274779.

3. Results

Between August 2014 and July 2016, 74 patients were recruited in 15 centers (Fig. 1 and Table 1). Seven patients were excluded for various reasons (lost to follow-up immediately after randomization and before any treatment: one; more than five lymph nodes: one; time between ADT and radiotherapy >3 mo: two; and only one PSA level before randomization and unacceptable PSA follow-up: three). Of the patients who were analyzed, 35 had received previous prostatic irradiation, mostly to the prostate bed (29 patients) or to the prostate (three patients, each following external beam radiotherapy or brachytherapy to the prostate). Only four patients presented with a concurrent local relapse. The median age was 67.7 yr. The median number of PET-positive oligorecurrent PLNs was one (interquartile range [IQR]: 1–2). Of note, 61% of patients only had one node visualized.

Acute toxicity and 1-yr toxicity were reported earlier [25]. At 2 yr, grade 2+ genitourinary and gastrointestinal toxicities were 10% and 2%, respectively (Table 2). No clinical parameters, such as a prior history of prostatic irradiation, could predict for 2-yr toxicity. Two patients suffered severe grade 3 incontinence occurring after combined prostatectomy and prostate bed irradiation. The completion rates for the quality of life questionnaires were 67% and 54% at 18 and 24 mo, respectively. No significant alteration in urinary or intestinal quality of life was noted at 2 yr (Fig. 2, and Supplementary Tables 1 and 2). Of note, no patient suffered from chronic grade 2 diarrhea or intestinal bleeding. Testosterone levels went back to normal levels in all patients except for one after a median time of 14.4 mo (Supplementary Fig. 1). Hormonal treatment–related quality of life and sexual activity were maintained at 2 yr. Reasons for not completing the quality of life form were independent of the patients in one of four cases (omission from the investigator staff). In other cases, participation could be related to patient health status. We compared age and baseline clinical characteristics of both respondents and nonrespondents at 24 mo, but there was no significant difference except for median PSA doubling time: 5.3 mo (IQR: 3.5–10.3 mo) in respondents versus 4.3 mo (IQR: 2.2–7.0 mo) in nonrespondents.

Table 1 – Patient characteristics, according to patient group

Patient and tumor characteristics	Group A + B (*n* = 31)	Group C + D (*n* = 36)	*p* value
Median age (yr)	68.0 (IQR: 64.0–72.0)	67.0 ± (IQR: 63.0–73.5)	0.9 (WMW)
ISUP score, *n* (%)			0.028 (F)
1	2 (6.4)	6 (17)	
2	7 (23)	16 (44)	
3	18 (58)	8 (22)	
>3	4 (13)	6 (17)	
Tumor stage, *n* (%)			0.11 (F)
pT1	2 (6.5)	–	
pT2	12 (39)	12 (33)	
pT3	17 (55)	18 (50)	
cT1	–	3 (8.3)	
cT2	–	3 (8.3)	
Pathological node involvement, *n* (%)			0.6 (F)
pN0	26 (84)	30 (83)	
pN1	1 (3.2)	–	
Nx	4 (13)	6 (17)	
Number of PET-positive PLN, *n* (%)			0.8 (F)
1	19 (61)	22 (61)	
2	7 (23)	9 (25)	
3	2 (6.4)	3 (11)	
4	2 (6.4)	1 (2.8)	
5	1 (3.2)	–	
Median PSA at baseline (ng/ml)	3.9 (IQR: 1.0–5.6)	3.6 (IQR:1.7–5.3)	0.9 (WMW)
Median PSA doubling time (mo)	4.6 (IQR: 3.2–9.2)	5.2 (IQR: 2.6–7.6)	0.9 (WMW)
Patients with prior administration of ADT, *n* (%)	2 (6.4)	10 (28)	0.028 (F)
Median time between diagnosis and initiation of the treatment being studied (mo)	27 (IQR: 9–62)	81 (IQR: 47–114)	<0.01 (WMW)

ADT = androgen depriving therapy; F = Fisher test; FCH = fluorocholine; IQR = interquartile range; ISUP = International Society of Urological Pathology; PET = positron-emission tomography; PLN = pelvic lymph node; PSA = prostate-specific antigen; WMW = Wilcoxon-Mann-Whitney test.
The trial population groups were as follows: group A: previous radical prostatectomy and no previous prostate bed radiation, with fewer than six FCH-PET–positive PLNs; group B: the same as group A, but with an FCH-PET–positive signal in the prostate bed, suggesting local relapse; group C: both previous radical prostatectomy and salvage prostate bed radiation therapy; and group D: previous irradiation of the prostate (brachytherapy or external beam radiotherapy). Patients in group A (28 of 67) and group B (four of 67) did not receive prior radiation therapy; patients in group C (29 of 67) and group D (six of 67) received prior prostatic bed and prostate-exclusive radiation therapy, respectively.

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Table 2 – Number of patients presenting residual 2-yr toxicity (*N*=50)

Toxicity	Baseline		2 yr	
	n	%	*n*	%
Anal and rectal toxicity				
Grade 1	1	1.5	7	14
Grade 2	–	–	2	4.0
Grade 3	–	–	–	–
Bowel toxicity				
Grade 1	1	1.5	8	16
Grade 2	–	–	1	2.0
Grade 3	–	–	–	–
Diarrhea				
Grade 1	2	3.0	4	8.0
Grade 2	–	–	–	–
Grade 3	–	–	–	–
Sexual toxicity				
Grade 1	–	–	2	4.0
Grade 2	1	1.5	4	8.0
Grade 3	–	–	1	2.0
Urinary toxicity				
Grade 1	11	16	18	36
Grade 2	1	1.5	3	6.0
Grade 3	–	–	2	4.0
Other				
Grade 1	22	33	23	46
Grade 2	17	25	2	4.0
Grade 3	2	3.0	–	–

When a patient presented several symptoms of different grades in the same category, only the maximal grade was taken into account. No grade 4 was reported. Other includes arterial hypertension in the vast majority of patients.

The median follow-up for survivors was 49.4 mo (IQR: 42.3–53.1 mo). The 2- and 3-yr PFS rates were 81% and 58%, respectively (Fig. 3A). Median PFS was 45.3 mo (95% CI: 31.8–48.5 mo). In all patients except for two, PSA decreased by >50% at 6 mo (Supplementary Fig. 2). We also performed a sensitivity analysis by applying the worst-case imputation method, where the four patients excluded from the analysis due to lack of follow-up were considered to have progressed 6 mo after treatment initiation. In this scenario, the median PFS was 41.8 mo and the 2-yr PFS was 76%. At 2 and 3 yr, the BRFS rates were of 58% and 46%, respectively (Fig. 4). The 2- and 3-yr time to secondary therapy initiation (TTST) was 84% and 63%, respectively (Fig. 3B). The median TTST was 49.8 mo. Median BRFS was 25.9 mo (Fig. 3C). The first secondary treatment at biochemical-clinical progression was stereotactic body radiotherapy (SBRT), ADT, or both in 22.5%, 42.5%, and 10% of patients, respectively. At relapse, 13%, 27%, and 25% of patients had progression with one metastasis, three or fewer metastases, and more than three metastases, respectively, while 7.5% had PSA progression only. Metastases were revealed by FCH-PET in 39% of patients, Ga-PSMA PET in 9%, and imaging methods other than PET in 4.5%. The relapses occurred in the lymph nodes outside the pelvis (M1a), bones (M1b), PLNs (N1), and prostatic bed in 50%, 30%, 25%, and 15% of patients, respectively (Table 3). Compared with groups A + B, progression for group C + D patients was as follows: M1a metastatic lymph nodes (39% vs 19%, $p = 0.081$), M1b bone metastases (28% vs 6.5%, $p = 0.028$), and prostatic bed local relapses (11% vs 6.5%, $p = 0.7$). The median TTADT was 51.9 mo (Supplementary Fig. 3). The 3-yr OS rate was 97% (two deaths), with one prostate cancer-related death at 33 mo after the beginning of treatment. No prognostic factor could predict for progression or biochemical complete response (Table 4 and Supplementary Table 3). We compared outcomes between groups based on prior therapy (Fig. 5 and Supplementary Fig. 4). In patients with prior prostatectomy, the 2-yr PFS rate was 97% in groups

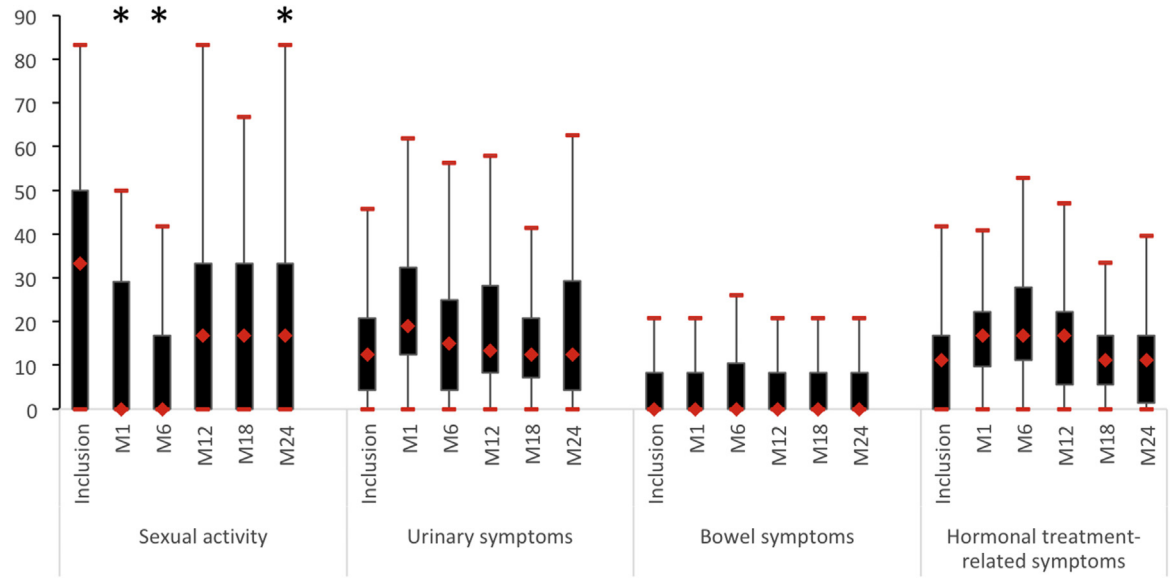

Fig. 2 – Quality of life (QLQ-PR25 scores) over time. Of 67 patients, 47 (70%) completed all assessments on time. Incontinence aid concerned only a minority of patients and is not shown. Sexual function concerned only a minority of the patients with sexual activity and is not shown. * Clinically and statistically significant difference.

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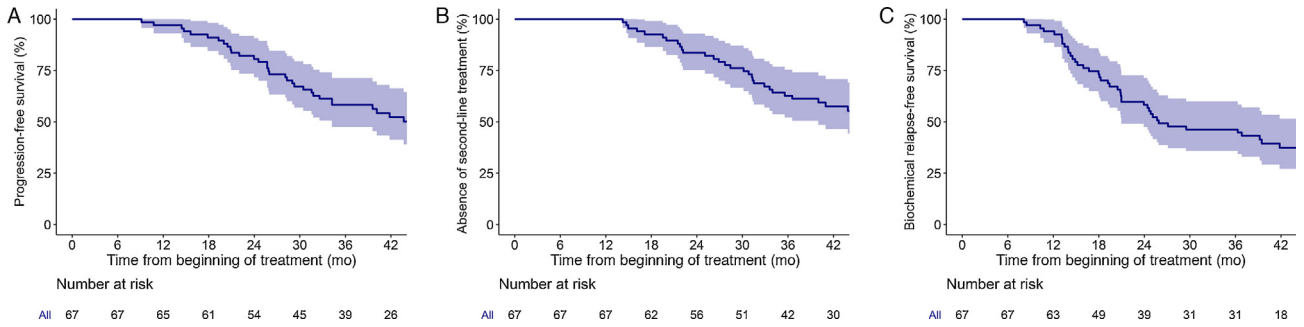

Fig. 3 – (A) Biochemical-clinical progression-free survival. (B) Time to start of a secondary treatment. (C) Biochemical relapse-free survival.

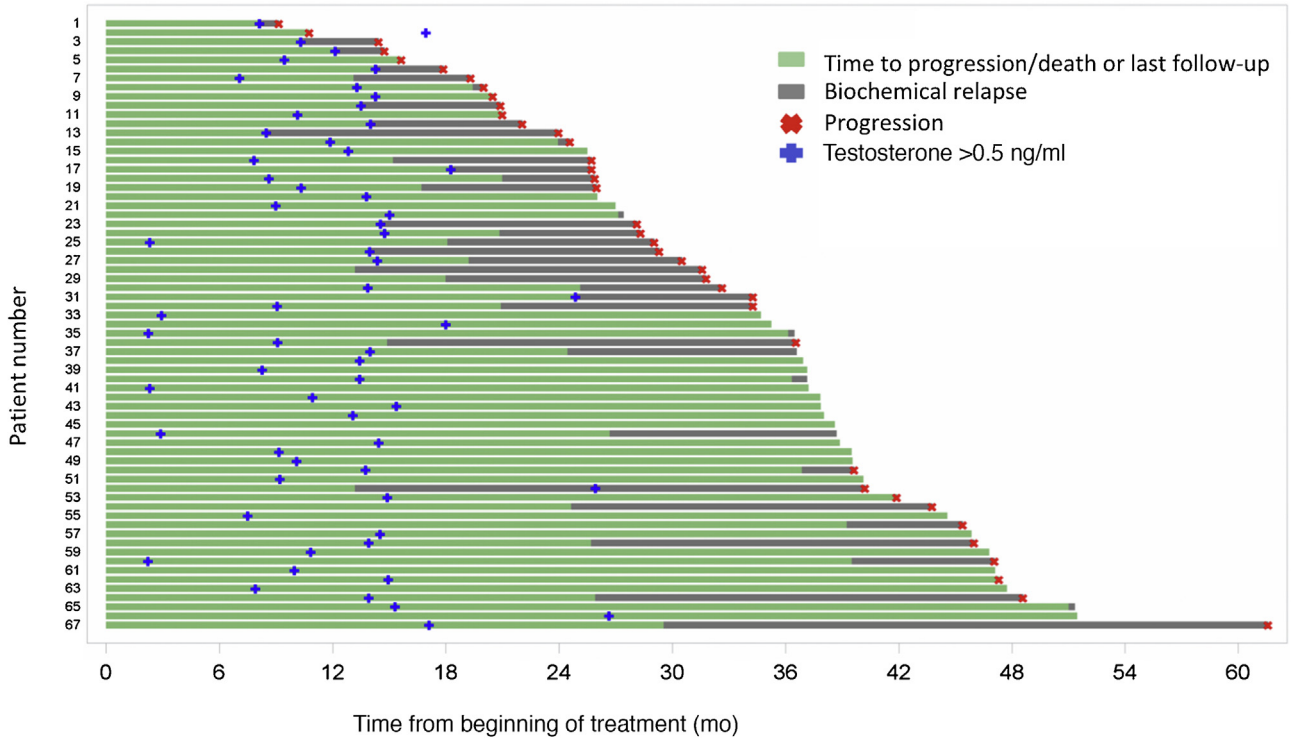

Fig. 4 – Swimmer plot of individual patient PSA response. Each bar represents one patient in the study. Biochemical relapse: PSA > 0.2 ng/ml after the post-treatment nadir. For patients with no history of prostatectomy: PSA level higher than nadir before treatment and >0.2 ng/ml following the post-treatment nadir. Progression was defined as a PSA value higher than the PSA level before treatment, confirmed by a second measurement and/or clinical progression as per RECIST 1.1 and/or death from any cause. PSA = prostate-specific antigen.

A + B versus 66% in group C ($p < 0.01$). The 2-yr metastasis-free survival (MFS) was 87%, and the MFS median was 48.2 (Supplementary Fig. 5).

4. Discussion

This trial addressed the use of 6-mo ADT combined with salvage high-dose pelvic radiotherapy in prostate cancer patients whose oligometastatic relapse had been identified on FCH-PET imaging. Our findings provide evidence of prolonged PFS in these patients at the cost of 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 elective pelvic radiotherapy combined with short-term ADT.

In the metastatic setting, ADT can be administered continuously or intermittently. In patients in whom metastases were diagnosed using conventional imaging (CT scan and total bone scan), continuous ADT is recommended, as the SWOG-9346 study was not able to rule out a 20% greater risk of death with intermittent therapy than with continuous therapy [23]. In patients with a rising PSA level and no visible metastases on conventional imaging, intermittent ADT was noninferior to continuous therapy [22]. In our situation, where conventional imaging would not have been able to detect metastatic lymph nodes, intermittent ADT could be considered a validated option. In this latter study, ADT was given for 8 mo and relapse was defined as clinical disease progression or PSA levels of >10 ng/ml [22]. Using this definition, the median time from

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Table 3 – Pattern of relapses at progression as assessed by the TNM 2005 classification for patients with (groups C+D) and without (groups A+B) prior prostate/prostatic bed radiotherapy

	Groups A + B (*N* = 31)		Groups C + D (*N* = 36)		*p* value
	n	%	*n*	%	
Prostatic bed	2	6.5	4	11	0.7 (F)
N1	5	16	5	14	1 (F)
M1a	6	19	14	39	0.081 (χ^2)
M1b	2	6.5	10	28	0.028 (F)
M1c	2	6.5	2	5.5	1 (F)
PSA progression only	–	–	5	14	0.057 (F)

PSA = prostate-specific antigen; F = Fisher test; FCH = fluorocholine; PET = positron-emission tomography; PLN = pelvic lymph node; TNM = tumor, node, metastasis.
Patients with metastases in separate anatomic regions were counted twice. The trial population groups were as follows: group A: previous radical prostatectomy and no previous prostate bed radiation, with fewer than six FCH-PET–positive PLNs; group B: the same as group A, but with an FCH-PET–positive signal in the prostate bed, suggesting local relapse; group C: both previous radical prostatectomy and salvage prostate bed radiation therapy; and group D: previous irradiation of the prostate (brachytherapy or external beam radiotherapy).

Table 4 – Predictors of progression

Parameter	*p* value	HR	95% HR CI
PSA at baseline (4 ng/ml)	0.2	0.88	0.70–1.09
ISUP at diagnosis (>4 vs ≤3)	0.6	1.24	0.52–2.96
Time from diagnosis to initiation of the treatment being studied (5 yr)	0.7	1.09	0.72–1.67
Number of nodes (>1 vs 1)	0.7	0.87	0.45–1.67
PSA doubling time (3 mo)	0.3	0.88	0.70–1.10
History of previous ADT	0.2	1.65	0.76–3.60
Treatment group (AB vs CD)	<0.01	0.34	0.17–0.68
Time to testosterone recovery (1 yr)	0.5	1.25	0.62–2.54

ADT = androgen depriving therapy; CI = confidence interval; HR = hazard ratio; ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen.

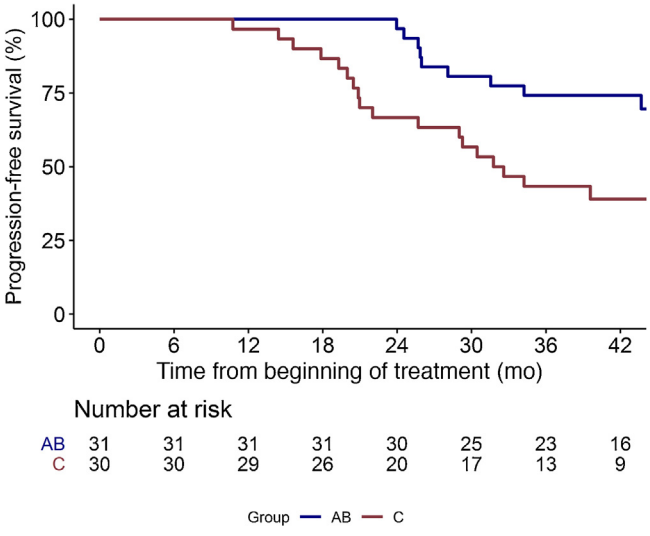

Fig. 5 – Biochemical-clinical progression-free survival according to groups A + B and C. The four trial population groups were as follows: Group A: previous radical prostatectomy and no previous prostate bed radiation, with fewer than six FCH-PET–positive PLNs; group B: the same as group A, but with an FCH-PET–positive signal in the prostate bed, suggesting local relapse; group C: both previous radical prostatectomy and salvage prostate bed radiation therapy; and group D: previous irradiation of the prostate (brachytherapy or external beam radiotherapy). Patients in group A (28 of 67) and group B (four of 67) did not receive prior radiation therapy; patients in group C (29 of 67) received prior prostatic bed radiation therapy. FCH = fluorocholine; PET = positron-emission tomography; PLN = pelvic lymph node.

initiation of ADT to progression was 28.1 mo. In our study, we chose 6 mo of ADT, as proposed by randomized trials in localized [26,27] or biochemically relapsing prostate cancer [28]. The relapse was observed at a median PSA level of 3.9 ng/ml (IQR: 2.4–4.9 ng/ml), lower than the 10 ng/ml cutoff in the PR7 study [22]. However, we found median PFS of 45.3 mo in our study and time to palliative ADT of 51.9 mo. This means that salvage radiotherapy combined with 6 mo of ADT may increase PFS, while delaying the need for palliative ADT. At 3 yr, 45% achieved a persistent complete response while achieving normal testosterone levels. Longer follow-up is needed to assess whether or not salvage radiotherapy combined with ADT is capable of perhaps even curing certain patients. A short PSA doubling time negatively predicted progression following ADT + ENRT. This patient population may benefit from prolonged ADT. Patients with a prior history of prostate bed irradiation had a worse outcome and presented with more bone metastases at relapse than patients with no prior radiotherapy. This might be explained by more frequent prior exposure to ADT in this group, which might have selected more biologically aggressive tumor clones. This further supports the early use of PLN irradiation in the RTOG 0534 SPPORT trial that showed improved MFS using combined salvage prostate bed and pelvic radiotherapy treatment [29]. In the future, the discovery of oligorecurrent metastatic PLNs may be less common as combined salvage

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prostate bed and pelvic radiotherapy will increasingly be used.

Importantly, tumor control was achieved at the cost of limited toxicity only. Despite high doses to lymph nodes close to the intestine or the bladder, grade 3 toxicity was infrequent, corroborating retrospective studies [14–18]. Despite a 1 cm gap between prostate bed and salvage pelvic radiation therapy fields, pelvic tissues were partially irradiated again, and this may have increased toxicity. Despite this, we did not observe increased toxicity between patients either with or without a past history of prostate radiotherapy. A similar tolerance profile has been reported in cases of repeated SBRT for pelvic oligorecurrences [30,31].

Metastasis-directed therapy using radiotherapy is an active area of research the positive impact of which on OS has been demonstrated in various primary histologies [32]. In pelvic nodal oligorecurrent prostate cancer specifically, radiotherapy can be administered either to the whole pelvis as proposed in our study or to the lymph nodes involved using SBRT. SBRT versus observation was shown to increase PFS and delay the need for ADT in both prospective randomized trials and retrospective analyses [6,33], with median distant PFS, TTST, and TTADT of around 20–28 mo, compared with 47–52 mo in our study. Similarly, median time to biochemical recurrence was 10 mo in the STOMP study and 25.9 mo in our study. We need to mention that our patient population comprised only those with oligorecurrence to PLNs and not to bone or abdominal lymph node metastases, the prognosis of which is worse. Lastly, in our study, PSA response was also longer because 6-mo-long ADT administration and testosterone recovered to noncastrate level after a median time of approximately 8 mo after the completion of treatment. However, this may also suggest that salvage high-dose elective pelvic radiotherapy may be superior to SBRT, as already suspected from retrospective studies [34,35]. Salvage lymphadenectomy has also been proposed for PLN oligorecurrences, at the cost of only limited toxicity. A pooled analysis of multiple series showed that complete biochemical response rates ranged from 13% to 79% (mean 44%). The 2-yr BRFS rates ranged from 23% to 64% [36], yielding results comparable with those of our study. Whether high-dose pelvic radiotherapy compares favorably with extended lymphadenectomy or whether both treatments need to be added remains an open question. An international randomized phase II trial (PEACE 5 – STORM, NCT03569241) is currently comparing 6-mo ADT and SBRT or lymphadenectomy with or without elective whole pelvis radiotherapy.

This trial has several limitations, the first being the limited number of patients inherent to the trial design. Second, FCH was the only radiotracer available when the study was initiated. Now, PSMA-based PET tracers are more widely available and may select patients with a more precise definition of the extension of the disease at biochemical relapse. However, despite the use of PSMA-based PET tracers, most patients relapse following stereotactic ablative radiotherapy to oligorecurrent disease [37], suggesting a role for combining systemic and radiotherapy-based local treatment. Moreover, the toxicity profile was good despite high-dose irradiation to the pelvis, but completion rate of the quality of life form was fairly low, which is a limitation. Our study also lacks genomic characterization of the tumors. Tumor mutational profiles can provide a biological definition of oligometastasis and may help select patients who may benefit from metastasis-directed treatments [38]. Lastly, this study was not randomized. The need for a randomized arm in phase 2 trials is highly debated. When the study started in 2014, very limited information on FCH-PET was available and the prevalence of oligorecurrent PLNs was unknown. We therefore decided to perform a single-arm phase 2 trial based on experts' recommendations [39] for cases when limited patients are available for recruitment. The only possibility for validating the benefits of adding salvage pelvic radiotherapy to a standard arm (intermittent ADT) will be an ongoing phase 3 study (OLIGOPELVIS 2 GETUG P12, NCT03630666). A standard arm in this situation is highly debated, as discussed during the Advanced Prostate Cancer Consensus Conference 2019 [40]. Recent trials showed that patients with metastatic prostate cancer benefit from androgen receptor agents such as abiraterone, apalutamide, or enzalutamide [41–43]. Future trials could also consider intensified androgen-axis blockade as a means of increasing tumor control in oligometastatic relapse of prostate cancer, especially in patients with a higher risk of relapse (short PSA doubling time or a prior history of prostate/prostate bed radiotherapy).

5. Conclusions

Combined high-dose elective salvage pelvic radiotherapy and ADT appeared to prolong tumor control in oligorecurrent pelvic node relapses in prostate cancer, with a significant proportion of patients still in complete remission 3 yr after the procedure, at the cost of only limited toxicity. Our study showed initial evidence of benefit, but a randomized trial is required to confirm this result.

***Author contributions*:** Stéphane Supiot had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Supiot, Campion.
Acquisition of data: Pasquier, Buthaud, Magné, Peiffert, Sargos, Crehange, Pommier, Loos, Hasbini, Latorzeff, Silva, Denis, Lagrange.
Analysis and interpretation of data: Supiot, Vaugier, Blanc-Lapierre.
Drafting of the manuscript: Supiot, Vaugier, Blanc-Lapierre.
Critical revision of the manuscript for important intellectual content: Supiot.
Statistical analysis: Blanc-Lapierre.
Obtaining funding: Supiot.
Administrative, technical, or material support: Vaugier.
Supervision: Supiot.
Other: None.

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Appendix A. Supplementary data

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References

[1] Colombie M, Campion L, Bailly C, et al. Prognostic value of metabolic parameters and clinical impact of (1)(8)F-fluorocholine PET/CT in biochemical recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2015;42:1784–93.
[2] Supiot S, Rousseau C. Oligometastatic prostate cancer: is it worth targeting the tip of the iceberg? Transl Cancer Res 2019;8(Suppl 2):S171–5.
[3] Calais J, Ceci F, Eiber M, et al. (18)F-fluciclovine PET-CT and (68)Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. Lancet Oncol 2019;20:1286–94.
[4] Lepinoy A, Cochet A, Cueff A, et al. Pattern of occult nodal relapse diagnosed with (18)F-fluoro-choline PET/CT in prostate cancer patients with biochemical failure after prostate-only radiotherapy. Radiother Oncol 2014;111:120–5.
[5] Tosoian JJ, Gorin MA, Ross AE, Pienta KJ, Tran PT, Schaeffer EM. Oligometastatic prostate cancer: definitions, clinical outcomes, and treatment considerations. Nat Rev Urol 2017;14:15–25.
[6] Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. J Clin Oncol 2018;36:446–53.
[7] Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol 2020;21:e18–28.
[8] Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. J Clin Oncol 2007;25:5366–73.
[9] Roach M, Moughan J, Lawton CAF, et al. Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): long-term results of a randomised, phase 3 trial. Lancet Oncol 2018;19:1504–15.
[10] Spiotto MT, Hancock SL, King CR. Radiotherapy after prostatectomy: improved biochemical relapse-free survival with whole pelvic compared with prostate bed only for high-risk patients. Int J Radiat Oncol Biol Phys 2007;69:54–61.
[11] Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. JAMA Oncol 2020;6:650–9.
[12] Ost P, Jereczek-Fossa BA, Van As N, et al. Pattern of progression after stereotactic body radiotherapy for oligometastatic prostate cancer nodal recurrences. Clin Oncol (R Coll Radiol) 2016;28:e115–20.
[13] Deek MP, Taparra K, Dao D, et al. Patterns of recurrence and modes of progression after metastasis-directed therapy in oligometastatic castration-sensitive prostate cancer. Int J Radiat Oncol Biol Phys 2021;109:387–95.
[14] Picchio M, Berardi G, Fodor A, et al. (11)C-choline PET/CT as a guide to radiation treatment planning of lymph-node relapses in prostate cancer patients. Eur J Nucl Med Mol Imaging 2014;41:1270–9.
[15] Fodor A, Berardi G, Fiorino C, et al. Toxicity and efficacy of salvage carbon 11-choline positron emission tomography/computed tomography-guided radiation therapy in patients with lymph node recurrence of prostate cancer. BJU Int 2017;119:406–13.
[16] Tran S, Jorcano S, Falco T, Lamanna G, Miralbell R, Zilli T. Oligorecurrent nodal prostate cancer: long-term results of an elective nodal irradiation approach. Am J Clin Oncol 2018;41:960–2.
[17] Ingrosso G, Mariucci C, Tenti MV, et al. Salvage radiotherapy in patients affected by oligorecurrent pelvic nodal prostate cancer. Clin Transl Oncol 2020;22:2236–43.
[18] Sato GE, Aizawa R, Nakamura K, et al. Long-term clinical outcomes of salvage pelvic radiation therapy for oligo-recurrent pelvic lymph nodes after definitive external-beam radiation therapy for non-metastatic prostate cancer. J Radiat Res 2020;61:622–8.
[19] Supiot S, Rio E, Pacteau V, Mauboussin MH, Campion L, Pein F. OLIGOPELVIS – GETUG P07: a multicentre phase II trial of combined salvage radiotherapy and hormone therapy in oligometastatic pelvic node relapses of prostate cancer. BMC Cancer 2015;15:646.
[20] Lawton CA, Michalski J, El-Naqa I, et al. RTOG GU Radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. Int J Radiat Oncol Biol Phys 2009;74:383–7.
[21] Sargos P, Guerif S, Latorzeff I, et al. Definition of lymph node areas for radiotherapy of prostate cancer: a critical literature review by the French Genito-Urinary Group and the French Association of Urology (GETUG-AFU). Cancer Treat Rev 2015;41:814–20.
[22] Crook JM, O'Callaghan CJ, Duncan G, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. N Engl J Med 2012;367:895–903.
[23] Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med 2013;368:1314–25.
[24] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343–6.
[25] Vaugier L, Palpacuer C, Rio E, et al. Early toxicity of a phase II trial of combined salvage radiotherapy and hormone therapy in oligometastatic pelvic node relapses of prostate cancer (OLIGOPELVIS GETUG P07). Int J Radiat Oncol Biol Phys 2019;103:1061–7.
[26] Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med 2011;365:107–18.
[27] D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. JAMA 2008;299:289–95.
[28] Carrie C, Magne N, Burban-Provost P, et al. Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial. Lancet Oncol 2019;20:1740–9.
[29] Pollack A, Karrison TG, Balogh AG, et al. Short term androgen deprivation therapy without or with pelvic lymph node treatment added to prostate bed only salvage radiotherapy: the NRG Oncology/RTOG 0534 SPPORT trial. Int J Radiat Oncol Biol Phys 2018;102:1605.
[30] Jereczek-Fossa BA, Beltramo G, Fariselli L, et al. Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. Int J Radiat Oncol Biol Phys 2012;82:889–97.

[31] Decaestecker K, De Meerleer G, Lambert B, et al. Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence. Radiat Oncol 2014;9:135.
[32] Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet 2019;393:2051–8.
[33] Siva S, Bressel M, Murphy DG, et al. Stereotactic ablative body radiotherapy (SABR) for oligometastatic prostate cancer: a prospective clinical trial. Eur Urol 2018;74:455–62.
[34] De Bleser E, Jereczek-Fossa BA, Pasquier D, et al. Metastasis-directed therapy in treating nodal oligorecurrent prostate cancer: a multi-institutional analysis comparing the outcome and toxicity of stereotactic body radiotherapy and elective nodal radiotherapy. Eur Urol 2019;76:732–9.
[35] Lepinoy A, Silva YE, Martin E, et al. Salvage extended field or involved field nodal irradiation in (18)F-fluorocholine PET/CT oligorecurrent nodal failures from prostate cancer. Eur J Nucl Med Mol Imaging 2019;46:40–8.
[36] Ploussard G, Gandaglia G, Borgmann H, et al. Salvage lymph node dissection for nodal recurrent prostate cancer: a systematic review. Eur Urol 2019;76:493–504.
[37] Kneebone A, Hruby G, Ainsworth H, et al. Stereotactic body radiotherapy for oligometastatic prostate cancer detected via prostate-specific membrane antigen positron emission tomography. Eur Urol Oncol 2018;1:531–7.
[38] Deek MP, Van der Eecken K, Phillips R, et al. The mutational landscape of metastatic castration-sensitive prostate cancer: the spectrum theory revisited. Eur Urol 2021, S0302-2838(20)31026-5.
[39] Gan HK, Grothey A, Pond GR, Moore MJ, Siu LL, Sargent D. Randomized phase II trials: inevitable or inadvisable? J Clin Oncol 2010;28:2641–7.
[40] Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced prostate cancer: report of the Advanced Prostate Cancer Consensus Conference 2019. Eur Urol 2020;77:508–47.
[41] James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:338–51.
[42] Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019;381:13–24.
[43] Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med 2019;381:121–31.

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