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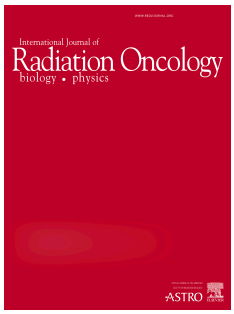

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Early toxicity of a phase II trial of combined salvage radiotherapy and hormone therapy in oligometastatic pelvic node relapses of prostate cancer (OLIGOPELVIS GETUG P07)

Short title : Early toxicity of the OLIGOPELVIS GETUG P07 trial

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Early toxicity of a phase II trial of combined salvage radiotherapy and hormone therapy in oligometastatic pelvic node relapses of prostate cancer (BLINDED)

Abstract

Purpose :

Limited pelvic nodal relapse of prostatic cancer is a paramount challenge for locoregional salvage treatments. Salvage whole pelvis radiotherapy as considered in the BLINDED trial, is an attractive option but with concerns about its toxicity. This article describes early toxicity with the technique.

Methods and Materials :

BLINDED was a prospective multi-center phase II trial investigating high-dose salvage pelvic irradiation with an additional dose to the fluorocholine-based positron-emission-tomography (FCH-PET)-positive pelvic lymph nodes (PLN), combined with six-month androgen blockade. The prescribed dose was 54 Gy in 1.8 Gy fractions with up to 66 Gy in 2.2 Gy fractions to the pathological PLN. Early toxicity was defined until one year after radiotherapy. Patients quality of life was assessed using the EORTC questionnaires (QLQ-C30 and QLQ-PR25).

Results :

Seventy-four patients were recruited in fifteen French radiation oncology departments between August 2014 and July 2016. Seven were excluded before treatment because of violation of the inclusion criteria. The intention-to-treat analysis therefore included sixty-seven patients. Half of them had received prior prostatic irradiation. Median age was 67.7 ± 6.5 years. Grade 2 acute urinary toxicity was observed in 9/67 patients (13.4%) and grade 2 one-year toxicity in 4/67 patients (6%). Three patients (4.4%) had grade 3 urinary toxicity. Grade 2 acute digestive toxicity was observed in 10/67 patients (14.9%) and grade 2 one-year toxicity in 4/67 patients (6%).
Patients with prior prostate bed irradiation did not exhibit increased urinary or digestive toxicity. EORTC questionnaire scores at one year did not worsen significantly.

Conclusions :

The acute and one-year toxicity of the BLINDED protocol was satisfactory, even in patients with a

past history of prostatic irradiation.

Keywords : pelvis salvage irradiation; urinary toxicity; bowel toxicity; prostate cancer; IMRT; IGRT; Fluorocholine PET; PSMA PET; pelvic reirradiation

1. Introduction

The development of new imaging techniques based on prostate-cancer specific markers such as fluorocholine positron-emission tomography (FCH-PET), has made identification of limited metastatic relapses of prostatic cancer feasible [1]–[3]. Among the various oligometastatic scenarios – a limited number of metastases (≤ 5 bone and/or lymph node metastases, with no visceral involvement) after previous prostate treatment – a pelvic lymph node (PLN) relapse is a paramount challenge, as an apparent turning point between still-controllable locoregional disease that can be managed without androgen blockade (through with salvage therapeutics) and diffuse disease for which androgen blockade would be the most appropriate treatment [4]–[5].

Salvage whole pelvis radiotherapy (WPRT) with an additional boost to any FCH-PET-positive PLN is an attractive option, but the best current evidence available is derived from retrospective studies on heterogeneous populations with heterogeneous treatment plans, though urinary and digestive toxicity was apparently acceptable [6]–[8]. Last but not least, despite prior prostatic bed radiotherapy as a first-line salvage treatment after radical prostatectomy or prostate-exclusive radiotherapy, a number of patients fulfilled the criteria of pelvic oligometastatic disease, and thus would potentially benefit from salvage pelvic reirradiation [9]. The question of the toxicity in this circumstance is even more pertinent.

The main objective of the multi-center phase II BLINDED trial (NCT BLINDED) [10] was to assess the efficacy of high-dose salvage WPRT in a prospective manner in a well-defined population. Prior prostatic irradiation was allowed. Here we present the early toxicity of this treatment, *ie* until one year after radiotherapy.

2. Materials and Methods

The BLINDED trial design has already been published [10]. The trial population was divided into four groups, each with a different treatment plan (see fig.1 for planning doses):

- Group A: prior radical prostatectomy and no prior prostate bed radiation, with fewer than five FCH-PET-positive PLN;
- Group B: as group A, but with also a FCH-PET-positive signal in the prostate bed, suggesting local relapse;
- Group C: with both previous radical prostatectomy and salvage prostate bed radiotherapy, thus entering a second round of salvage therapy in the BLINDED trial;
- Group D : with prior conservative prostate treatment (external-body radiation or brachytherapy).

Image-guided intensity-modulated radiation (IG-IMRT) was required to deliver 54 Gy in 1.8 Gy fractions, with up to 66 Gy in 2.2 Gy fractions to the pathological PLN with simultaneous integrated boost (SIB). Patients who had not received prior 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. Androgen blockade was achieved by LH-RH agonist or antagonist injections during six months, ideally administered on the first day of radiotherapy, or within the three months prior to the first day of radiotherapy [10].

Acute toxicity was defined as events occurring between the first week of radiotherapy and one month after the end of radiotherapy (M1). Later events were documented from M1 until one year after radiotherapy in the present study. If a patient presented the same toxic event several times, only the higher grade event was analyzed. All toxicities were graded according to the CTCAE v4.0 classification.

Patient quality of life was evaluated at inclusion (baseline) and at M6 with the QLQ-C30 v3 and the prostate cancer module QLQ-PR25 questionnaires of the EORTC [11].

Sixty-three (+ 10%) evaluable patients were required to achieve adequate statistical power [10]. The primary outcome (not reported here) was biochemical relapse-free survival at two years.

Data from all evaluable patients was analyzed. Baseline and six-month quality of life scores were compared using a Wilcoxon signed test for matched pairs. A Benjamini-Hochberg procedure was applied to control for false discovery rate. For all analyses, a p-value of less than 0.05 was considered as statistically significant. All reported p-values are two sided. Quality of life differences were considered as clinically relevant when greater than 10 [11].

3.Results

Seventy-five patients in 15 French oncology centers were assessed for eligibility from August 2014 until July 2016. Sixty-seven patients (median age, 67.7 ± 6.5 years) were analyzed in intention-to-treat (fig. 2). Patient characteristics and staging at diagnosis are summarized in table 1. Sixty-one patients (91%) were initially treated by radical prostatectomy (groups A, B and C). Twenty-nine of the sixty-seven patients (43.3%) received first-line salvage prostate bed radiation (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 (83.5%) had one or two positive pelvic lymph nodes at relapse. Four patients in group B, with no prior radiotherapy, had a local relapse in the prostate bed.

Acute genitourinary toxicity was dominated by grade 1 urinary urgency (33/67 patients, 49.2%) (fig.

3). The frequency of genito-urinary events at one year globally decreased in comparison to M1 (32.8% (22/67) grade 1 urinary urgency; 3% (2/67) grade 2; 25.3% (17/67) grade 1 urinary incontinence). Three patients (4.4%) reported grade 3 urinary incontinence and one of them grade 3 hematuria. No urinary incontinence was then reported at one year but grade 2 hematuria and grade 2 urinary urgency ; one group B patient developped grade 3 urinary incontinence with grade 3 hematuria at one year, leading to the discovery of a bladder papillary carcinoma (pTa); one group C patient reported isolated grade 3 urinary incontinence at one year without earlier symptoms.

Around 67% of the patients (45/67) were affected by acute moderate diarrhea: 55.2% (37/67) grade 1 and 11.9% (8/67) grade 2. Around 34% of the patients (23/67) reported moderate grade 1 abdominal pain, constipation, bloating or flatulence. At one year : around 30 % (20/67) reported grade 1 digestive inconvenience. There was only one grade 2 (1.5%) diarrhea and one grade 2 (1.5%) anal without abdominal upset. Two patients (3%) suffered from grade 2 rectal bleeding.

Pooling the patients who had not previously undergone radiotherapy (groups A and B) versus the others (groups C and D), there were no notable differences regarding the acute or later toxicity (fig. 3 and supplementary for details).

There were no cardiovascular events, but a moderate worsening of hypertension.

Regarding the quality of life evaluation : the completion rates for the QLQ-C30 and QLQ-PR25 questionnaires between baseline and one year was around 70%. There were no significant changes among the items of the QLQ-C30, in particular to physical or cognitive functioning (supplementary materials). Dyspnea and role functioning were the only symptoms to worsen to a not clinically relevant level but statistically significant degree between baseline and M6 ($p = 0.0260$ and 0.0468 respectively), but disappeared at one year. There were no significant differences for urinary, bowel-

related symptoms (p = 1.0000 and p = 0.5726 respectively) and sexual activity (p = 0.1152) for the QLQ-PR25 scores at one year (fig. 3). At six months, a statistically – and clinically – significant worsening in sexual activity was observed (p = 0.0020, medium value of +16.6 points) as well as for expected androgen blockade-related symptoms (p = 0.0080, medium value of -5.6 points).

4. Discussion

Global tolerance of the BLINDED protocol was satisfactory, in line with retrospective data for high-dose salvage WPRT in the literature [12]–[14], even in patients with a past history of prostatic irradiation.

Based on the measurements of the EORTC questionnaires, patient quality of life did not significantly worsen between baseline and one year. Sexual activity significantly decreased at six months, due to the androgen blockade-related castration. The increase in dyspnea at six months for 25% of the patients — although not clinically relevant and not present later — may also be attributed to androgen blockade as previously described in the literature [11].

Fifty-two per cent of patients had previous prostate bed or prostate exclusive radiotherapy. Bladder, sigmoid colon and small bowel ran the risk of being partially reirradiated. There were no increased urinary or digestive toxicity in these patients compared to those who had not previously been irradiated. These results are coherent with those from the other studies that considered pelvic reirradiation using stereotactic body radiotherapy [15]–[17] or even within the context of salvage WPRT directed by FCH-PET imaging [8]. Further study of the repair mechanisms in radiation injury to the pelvic tissues, and hence the feasibility of reirradiation, is highly recommended.

We should emphasize that the toxicity reported in this paper is based on an evaluation period of one

year. Further evaluation after a longer follow-up period is required [18]. The limited number of patients also constitutes a weakness.

5. Conclusions

Rates of acute and one year urinary and digestive toxicity following whole-pelvis salvage irradiation with boost to oligometastatic FCH-PET-positive lymph nodes of prostate adenocarcinoma are acceptable. The moderate and transitory worsening of hypertension and sexual activity—but not digestive or bladder-related function—may be attributed to the combined androgen deprivation treatment. Later toxicity rates will be reported together with the treatment efficiency. The phase III BLINDED trial, which will compare these pelvic salvage strategies to long-term androgen blockade, will provide further data on the toxicity of these treatments.

6. Acknowledgements

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Figures :

Fig. 1 : (color online) 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.

Fig. 2 : Trial flow chart. RP = radical prostatectomy; PB = prostatic bed; (EB)RT = (external beam) radiotherapy; BT = brachytherapy

Fig. 3 : (color online) Panel A : Number of patients with gastrointestinal (left) and genitourinary (right) CTCAE v4.0 toxic events at M1 (≤ 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 (28/67) and Group B (4/67) did not receive prior radiotherapy; patients of Group C (29/67) and Group D (6/67) respectively received prior prostatic bed and prostate-exclusive radiotherapy.

Panel B : QLQ-PR25 score differences with time. 47/67 patients (70%) completed all assessments with time. Incontinence aid only concerned a minority of patients and is not

shown. Sexual functioning only concerned a minority of the patients with sexual activity and is not shown.

Min = minimal difference, Max = maximal difference, Q1 = first quartile, Q3 = third quartile.

Tables

		(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)		28 (41.8%)
Group B (RP)		4 (6.0%)
Group C (RP + PB-EBRT)		29 (43.3%)
Group D (prostate conservative)		
	EBRT	3 (4.5%)
	BT	3 (4.5%)
Number of pathological PLN		
	1	37 (55.2%)
	2	19 (28.3%)
	3	7 (10.4%)
	4	3 (4.5%)
	5	1 (1.5%)
Baseline characteristics		
Median age (years)		67.7 ± 6.5

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 1 : Initial prostatic adenocarcinoma staging (TNM 2005) and baseline characteristics of the patients.

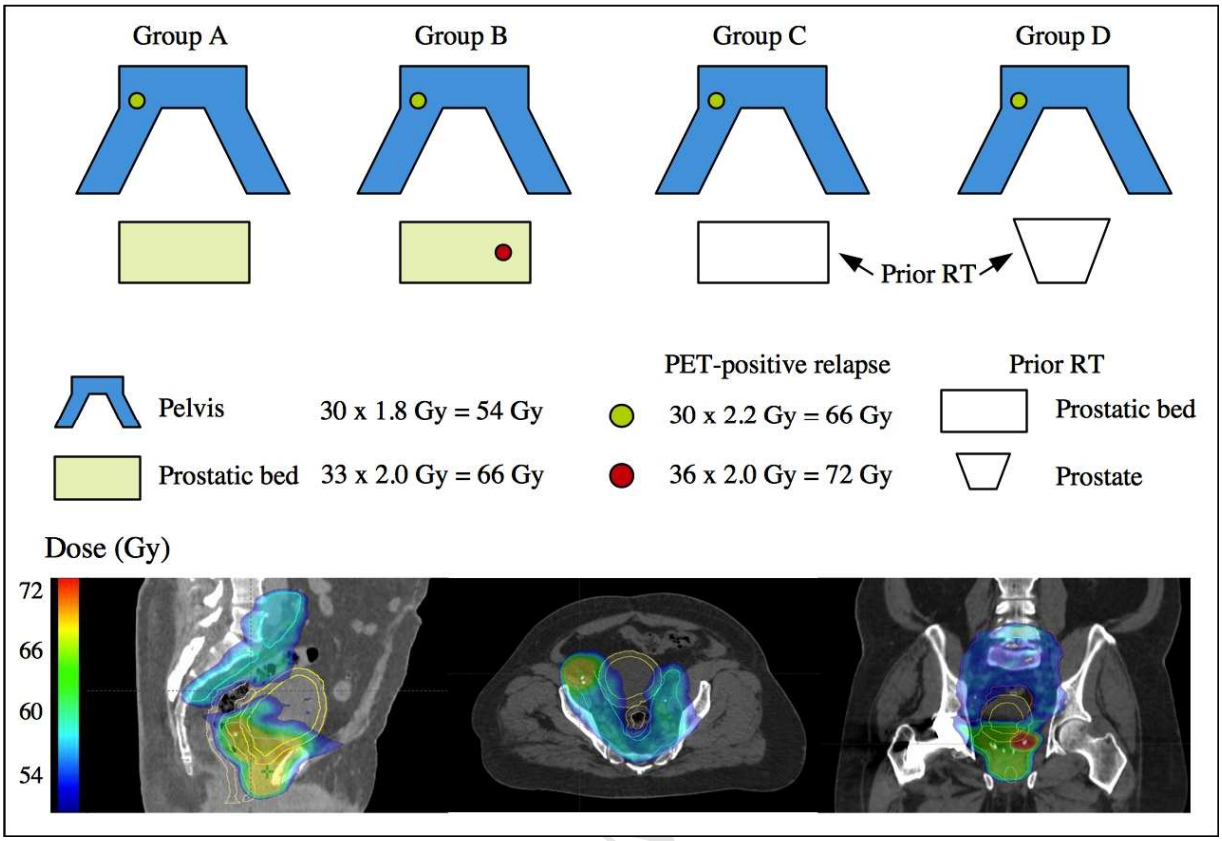
RP (radical prostatectomy); PB (prostatic bed); EBRT (external-beam radiotherapy); BT (brachytherapy); PLN (pelvic lymph node). Digestive comorbidities : gastric ulcer, gastro-esophageal reflux, colonic polyps. Abdominal surgery : appendice, gall bladder, haemorrhoids, sigmoid colon. Radical prostatectomy was not counted. Quantitative variables : mean ± standard deviation. Qualitative variables : number of subjects (%).

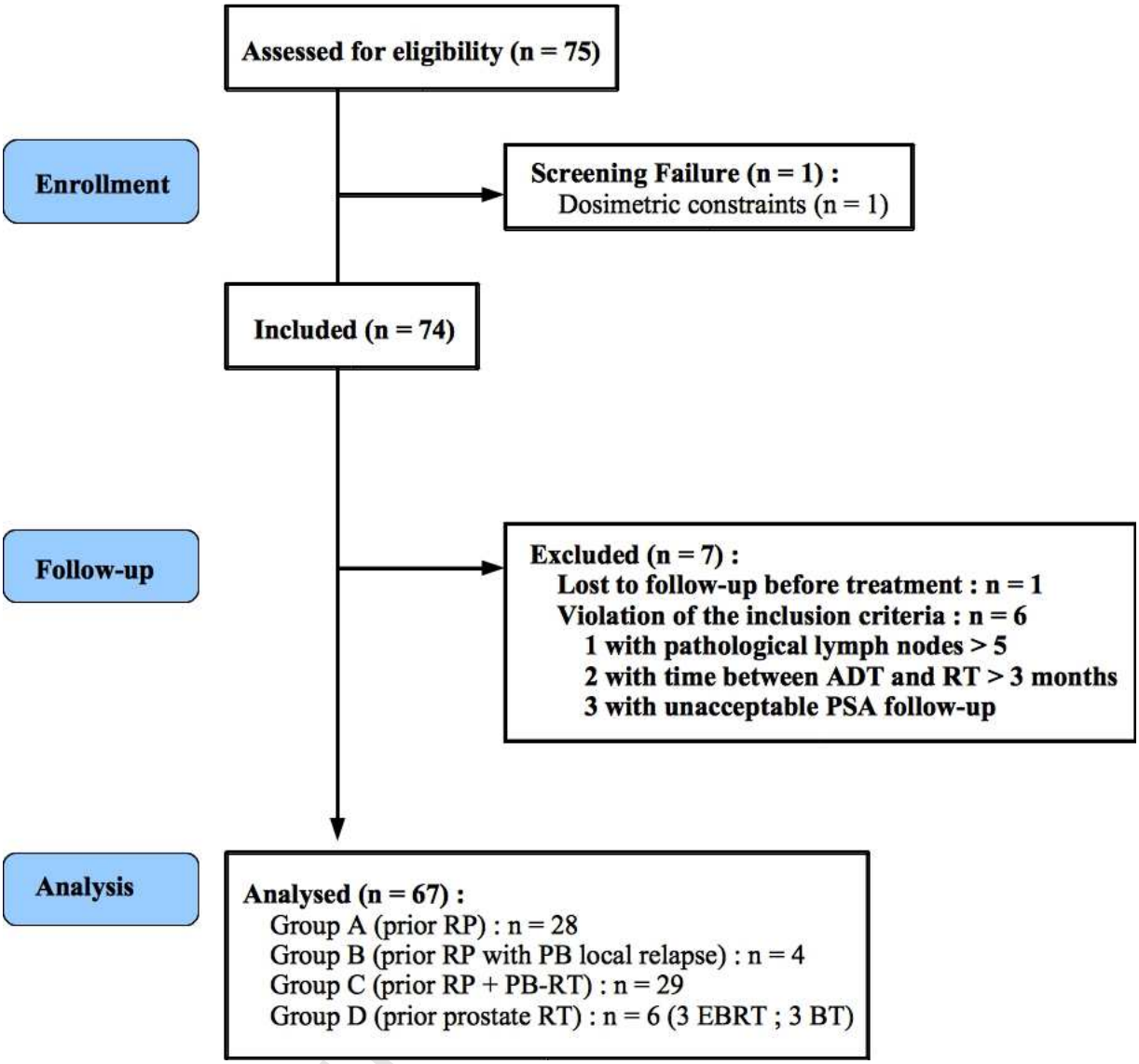
				(n = 67)					(n = 67)
Gastrointestinal	**Grade**	1	2	3	**Genitourinary**	**Grade**	1	2	3
Inconvenience	Baseline	1 (1.5%)	-	-	**Urgencies**	Baseline	7 (10.4%)	1 (1.5%)	-
	M1	21 (31.3%)	2 (3.0%)	-		M1	33 (49.2%)	8 (11.9%)	-
	1-year	11 (16.4%)	-	-		1-year	22 (32.8%)	2 (3.0%)	-
Diarrhea	Baseline	2 (3.0%)	-	-	**Incontinence**	Baseline	7 (10.4%)	-	-
	M1	37 (55.2%)	8 (11.9%)	-		M1	13 (19.4%)	2 (3.0%)	-
	1-year	10 (14.9%)	1 (1.5%)	-		1-year	17 (25.3%)	-	3 (4.4%)
Bleeding	Baseline	-	-	-	**Hematuria**	Baseline	-	-	-
	M1	4 (5.9%)	1 (1.5%)	-		M1	3 (4.4%)	-	-
	1-year	4 (5.9%)	2 (3.0%)	-		1-year	2 (3.0%)	2 (3.0%)	1 (1.5%)
Proctitis	Baseline	1 (1.5%)	-	-	**Pain**	Baseline	-	-	-
	M1	12 (17.9%)	2 (3.0%)	-		M1	7 (10.4%)	-	-
	1-year	5 (7.4%)	1 (1.5%)	-		1-year	-	-	-
Pts with tox.	Baseline	2 (3.0%)	-	-	**Dysuria**	Baseline	-	-	-
	M1	47 (70.1%)	10 (14.9%)	-		M1	3 (4.4%)	-	-
	1-year	20 (29.8%)	4 (5.9%)	-		1-year	-	1 (1.5%)	-
					Pts with tox.	Baseline	12 (17.9%)	1 (1.5%)	-
						M1	40 (59.7%)	9 (13.4%)	-
						1-year	32 (47.7%)	4 (5.9%)	3 (4.4%)
Cardiovascular	**Grade**	1	2	3					
Hypertension	Baseline	29 (43.3%)	19 (28.3%)	6 (8.9%)					
	M1	12 (17.9%)	31 (46.2%)	12 (17.9%)					
	1-year	19 (28.3%)	15 (22.4%)	1 (1.5%)					

Table 2 : Baseline, M1 (≤ 1 month after the end of radiotherapy) and one-year urinary, digestive and cardiovascular events. A patient may present several symptoms. Example : a patient may have a grade 1 diarrhea and grade 2 digestive bleeding at M1. He thus would be counted in grade 1 and

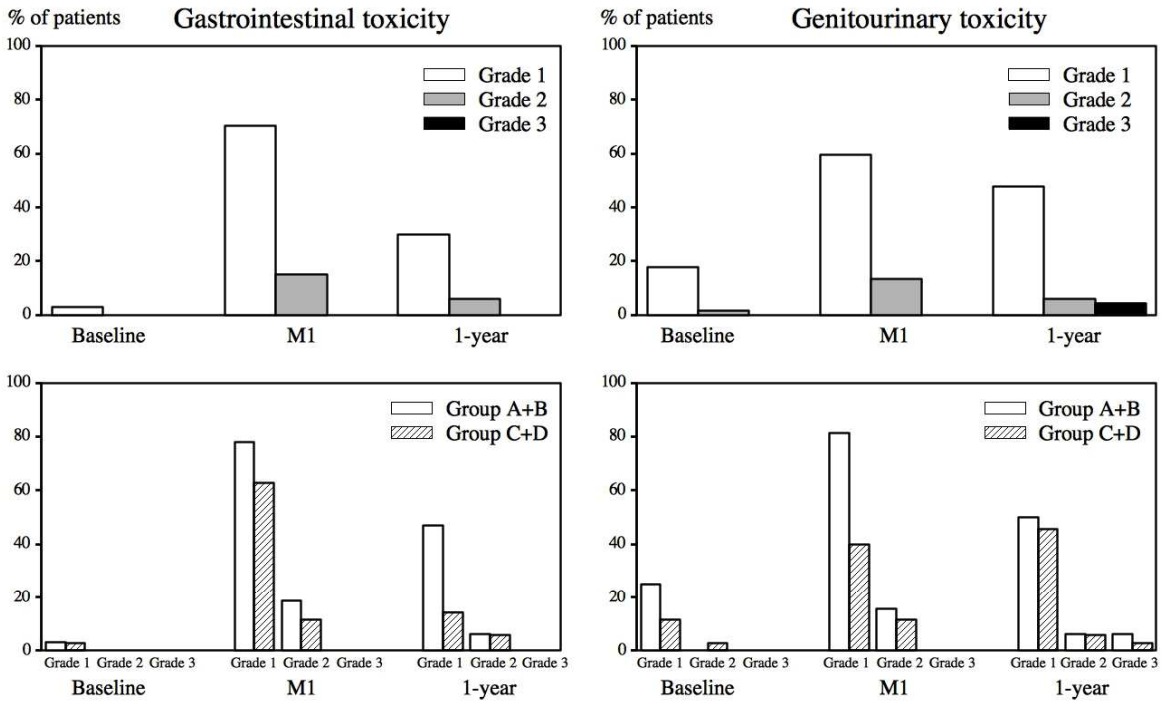
grade 2 number of patients with digestive toxicity at M1 (Pts with tox.). No grade 4 were reported.

Digestive inconvenience : constipation, flatulences, bloating, pain. Proctitis : haemorrhoids, anal pain.

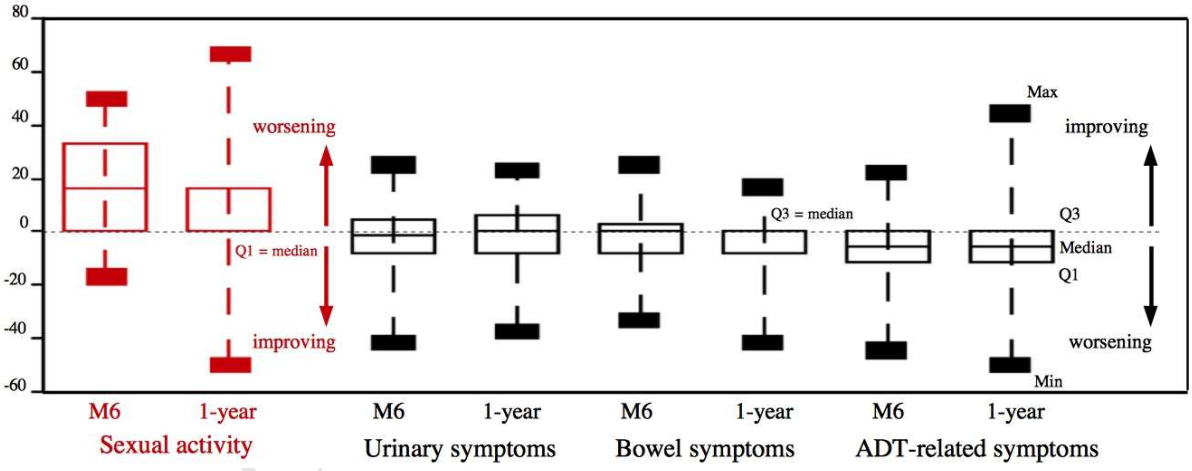



Assessed for eligibility (n = 75)
Enrollment
Screening Failure (n = 1) :
Dosimetric constraints (n = 1)
Included (n = 74)
Follow-up
Excluded (n = 7) :
Lost to follow-up before treatment : n = 1
Violation of the inclusion criteria : n = 6
1 with pathological lymph nodes > 5
2 with time between ADT and RT > 3 months
3 with unacceptable PSA follow-up
Analysis
Analysed (n = 67) :
Group A (prior RP) : n = 28
Group B (prior RP with PB local relapse) : n = 4
Group C (prior RP + PB-RT) : n = 29
Group D (prior prostate RT) : n = 6 (3 EBRT ; 3 BT)

A.



B. QLQ-PR25 Score Differences



Early toxicity of the BLINDED trial

Summary

As the benefits of salvage pelvic radiotherapy in biochemically-recurrent prostate cancer following radical therapy is still unkown, the toxicity of such strategy matters.

BLINDED was a prospective multicenter phase II trial investigating a combination of six months androgen blockade with high-dose IG-IMRT salvage irradiation in pelvic oligometastatic patients detected by 18F-choline PET imaging.

Early toxicity until one year after radiotherapy was acceptable, in particular in patients with a past history of prostatic irradiation.