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Scientific Letter

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)

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Summary

As the benefits of salvage pelvic radiation therapy in biochemically recurrent prostate cancer after radical therapy are still unknown, the toxicity of such a strategy matters. OLIGOPELVIS GETUG P07 was a prospective multicenter phase 2 trial investigating a combination of 6 months of androgen blockade with high-dose image guided intensity modulated radiation therapy salvage irradiation in patients with pelvic oligometastasis detected by 18F-choline positron emission tomography imaging. Early toxicity until 1 year after radiation therapy was acceptable, in particular in patients with a history of prostatic irradiation.

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

Methods and Materials: BLINDED was a prospective multicenter phase 2 trial investigating high-dose salvage pelvic irradiation with an additional dose to the fluorocholine-based positron emission tomography−positive pelvic lymph nodes, combined with 6-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 pathologic pelvic lymph nodes. Early toxicity was defined as toxicity until 1 year after radiation therapy. Patients quality of life was assessed using the European Organisation for Research and Treatment of Cancer questionnaires (QLQ-C30 and QLQ-PR25).

Results: Seventy-four patients were recruited in 15 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 67 patients. Half had received prior prostatic irradiation. Median age was 67.7 ± 6.5 years. Grade 2 acute urinary toxicity was observed in 9 of 67 patients (13.4%), and grade 2 1-year toxicity occurred in 4 of 67 patients (6%). Three patients (4.4%) had grade 3 urinary toxicity. Grade 2 acute digestive toxicity was observed in 10 of 67 patients (14.9%), and grade 2 1-year toxicity occurred in 4 of 67 patients (6%). Patients with prior prostate bed irradiation did not exhibit increased urinary or digestive toxicity. The European Organisation for Research and Treatment of Cancer questionnaire scores at 1 year did not worsen significantly.

Conclusions: The acute and 1-year toxicity of the BLINDED protocol was satisfactory, even in patients with a history of prostatic irradiation.

Introduction

The development of new imaging techniques based on prostate cancer−specific markers such as fluorocholine (FCH) positron emission tomography (PET) has made identification of limited metastatic relapses of prostate 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 radiation therapy (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, although urinary and digestive toxicity was apparently acceptable.[6-8] Last but not least, despite prior prostatic bed radiation therapy as a first-line salvage treatment after radical prostatectomy or prostate-exclusive radiation therapy, a number of patients fulfilled the criteria for 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 multicenter phase 2 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 1 year after radiation therapy).

Methods and Materials

The BLINDED trial design has already been published.[10] The trial population was divided into 4 groups, each with a different treatment plan (see Fig. 1 for planning doses):

(1) Group A: prior radical prostatectomy and no prior prostate bed radiation, with fewer than 5 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: with both previous radical prostatectomy and salvage prostate bed radiation therapy, thus entering a second round of salvage therapy in the BLINDED trial; and
(4) Group D: with prior conservative prostate treatment (external body radiation or brachytherapy).

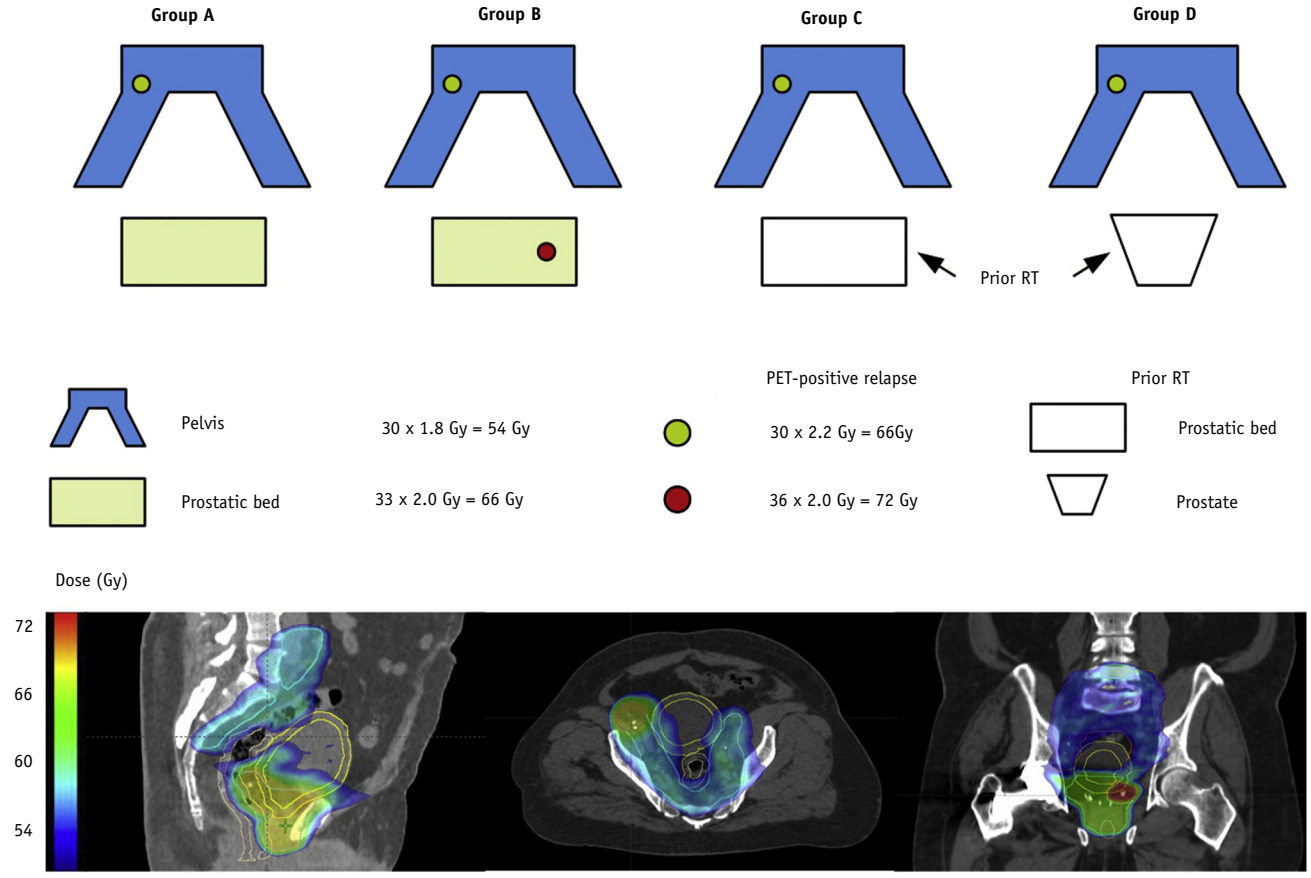

Fig. 1. Top panel: Schematic view of the patient population and treatment planning options. Prior radiation therapy (RT) for Group C: prior RT of the prostatic bed. Prior RT for Group D: prior prostate RT (external beam or brachytherapy). Bottom panel: Example of the treatment planning for 1 patient of Group B with fluorocholine-based positron emission tomography−positive node into the right external iliac vessels and 1 left posterior local relapse into the prostatic bed. Delineations of whole pelvic lymph nodes, bladder, and rectum walls are shown.

Image guided intensity modulated radiation was required to deliver 54 Gy in 1.8 Gy fractions, with up to 66 Gy in 2.2 Gy fractions to the pathologic PLN with simultaneous integrated boost. 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 Luteinizing Hormone Releasing Hormone (LH-RH) agonist or antagonist injections for 6 months, ideally administered on the first day of radiation therapy or within the 3 months before the first day of radiation therapy.[10]

Acute toxicity was defined as events occurring between the first week of radiation therapy and 1 month after the end of radiation therapy (M1). Later events were documented from M1 until 1 year after radiation therapy in the present study. If a patient presented with the same toxic event several times, only the highest grade event was analyzed. All toxicities were graded according to the Common Terminology Criteria for Adverse Events 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 European Organisation for Research and Treatment of Cancer.[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 2 years.

Data from all evaluable patients were analyzed. Baseline and 6-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 .05 was considered statistically significant. All reported P values are 2 sided. Quality of life differences were considered as clinically relevant when greater than 10.[11]

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 an intention-to-treat analysis (Fig. 2). Patient

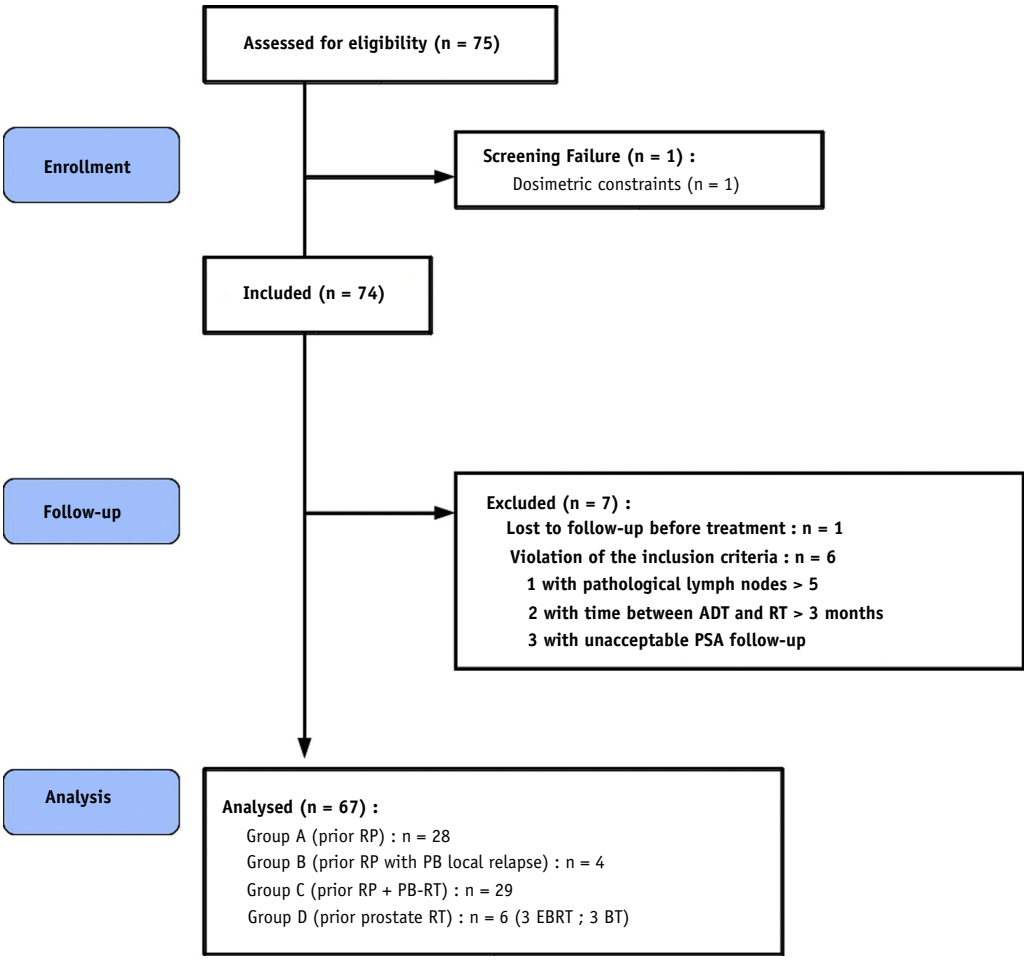

Fig. 2. Trial flow chart. *Abbreviations:* BT = brachytherapy; (EB)RT = (external beam) radiation therapy; PB = prostatic bed; RP = radical prostatectomy.

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 67 patients (43.3%) received first-line salvage prostate bed radiation (group C). Only a minority of patients (9%, 6 of 67) had been previously treated conservatively (Group D): 3 were treated with external beam radiation therapy at a mean dose of 74 Gy (70-76 Gy), and 3 had received prostate brachytherapy. A substantial majority (83.5%) had 1 or 2 positive PLNs at relapse. Four patients in group B, with no prior radiation therapy, had a local relapse in the prostate bed.

Acute genitourinary toxicity (Table 2) was dominated by grade 1 urinary urgency (33 of 67 patients, 49.2%) (Fig. 3). The frequency of genitourinary events at 1 year globally decreased in comparison to M1 (32.8% [22/67] grade 1 urinary urgency and 3% [2/67] grade 2; 25.3% [17/67] grade 1 urinary incontinence). Three patients (4.4%) reported grade 3 urinary incontinence and 1 of whom had grade 3 hematuria. No urinary incontinence was reported at 1 year, but grade 2 hematuria and grade 2 urinary urgency were reported; 1 group B patient developed grade 3 hematuria at 1 year, leading to the discovery of a bladder papillary carcinoma (pTa); 1 group C patient reported isolated grade 3 urinary incontinence at 1 year without earlier symptoms.

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. Around 34% of the patients (23 of 67) reported moderate grade 1 abdominal pain, constipation, bloating, or flatulence. At 1 year, approximately 30% (20 of 67) reported grade 1 digestive inconvenience. There was only 1 grade 2 (1.5%) diarrhea and 1 grade 2 (1.5%) anal pain without abdominal upset. Two patients (3%) experienced grade 2 rectal bleeding.

Pooling the patients who had not previously undergone radiation therapy (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 Materials, Supplementary Tables 1 and 2 available online at https://doi.org/10.1016/j.ijrobp.2018.12.020). There were no cardiovascular events, but a moderate worsening of hypertension was noted.

Regarding the quality of life evaluation: The completion rates for the QLQ-C30 and QLQ-PR25 questionnaires between baseline and 1 year was around 70%. There were no significant changes among the items of the QLQ-C30,

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

Staging and characteristics	(n = 67)
Initial prostate staging	
Gleason score	7 ± 0.8
Pathologic tumor stage	
pT1	2 (3.0%)
pT2	24 (35.8%)
pT3	35 (52.2%)
cT1	3 (4.5%)
cT2	3 (4.5%)
Pathologic 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%)
No. of pathologic 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 (y)	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%)

Abbreviations: BT = brachytherapy; EBRT = external beam radiation therapy; ECOG = Eastern Cooperative Oncology Group; PB = prostatic bed; PLN = pelvic lymph node; RP = radical prostatectomy.

Digestive comorbidities: gastric ulcer, gastro-esophageal reflux, colonic polyps. Abdominal surgery: appendix, gall bladder, hemorrhoids, sigmoid colon. Radical prostatectomy was not counted. Qualitative variables: number of subjects (%). Quantitative variables: mean ± standard deviation.

Table 2 Baseline, M1 (≤1 month after the end of radiation therapy), and 1-year urinary, digestive, and cardiovascular events

Events (n = 67)	Grade	1	2	3
Gastrointestinal				
Inconvenience	Baseline	1 (1.5%)	-	-
	M1	21 (31.3%)	2 (3.0%)	-
	1-year	11 (16.4%)	-	-
Diarrhea	Baseline	2 (3.0%)	-	-
	M1	37 (55.2%)	8 (11.9%)	-
	1-year	10 (14.9%)	1 (1.5%)	-
Bleeding	Baseline	-	-	-
	M1	4 (5.9%)	1 (1.5%)	-
	1-year	4 (5.9%)	2 (3.0%)	-
Proctitis	Baseline	1 (1.5%)	-	-
	M1	12 (17.9%)	2 (3.0%)	-
	1-year	5 (7.4%)	1 (1.5%)	-
Pts with tox.	Baseline	2 (3.0%)	-	-
	M1	47 (70.1%)	10 (14.9%)	-
	1-year	20 (29.8%)	4 (5.9%)	-
Cardiovascular				
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%)
Genitourinary				
Urgency	Baseline	7 (10.4%)	1 (1.5%)	-
	M1	33 (49.2%)	8 (11.9%)	-
	1-year	22 (32.8%)	2 (3.0%)	-
Incontinence	Baseline	7 (10.4%)	-	-
	M1	13 (19.4%)	2 (3.0%)	-
	1-year	17 (25.3%)	-	3 (4.4%)
Hematuria	Baseline	-	-	-
	M1	3 (4.4%)	-	-
	1-year	2 (3.0%)	2 (3.0%)	1 (1.5%)
Pain	Baseline	-	-	-
	M1	7 (10.4%)	-	-
	1-year	-	-	-
Dysuria	Baseline	-	-	-
	M1	3 (4.4%)	-	-
	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%)

Example: A patient may have grade 1 diarrhea and grade 2 digestive bleeding at M1; this patient would be counted in the grade 1 and grade 2 number of patients with digestive toxicity at M1 (Pts with tox). No grade 4 were reported. Digestive inconvenience: constipation, flatulence, bloating, pain. Proctitis: hemorrhoids, anal pain.

in particular to physical or cognitive functioning (Supplementary Materials; Supplementary Tables 4 and 5 and Supplementary figure 1 available online at https://doi.org/10.1016/j.ijrobp.2018.12.020). Dyspnea and role functioning were the only symptoms to worsen to a not clinically relevant level but statistically significant degree between baseline and M6 ($P = .0260$ and .0468, respectively), symptoms resolved at one year. There were no significant differences for urinary, bowel-related symptoms ($P = 1.0000$ and $P = .5726$, respectively) and sexual activity ($P = .1152$) for the QLQ-PR25 scores at 1 year (Fig. 3). At 6 months, a statistically—and

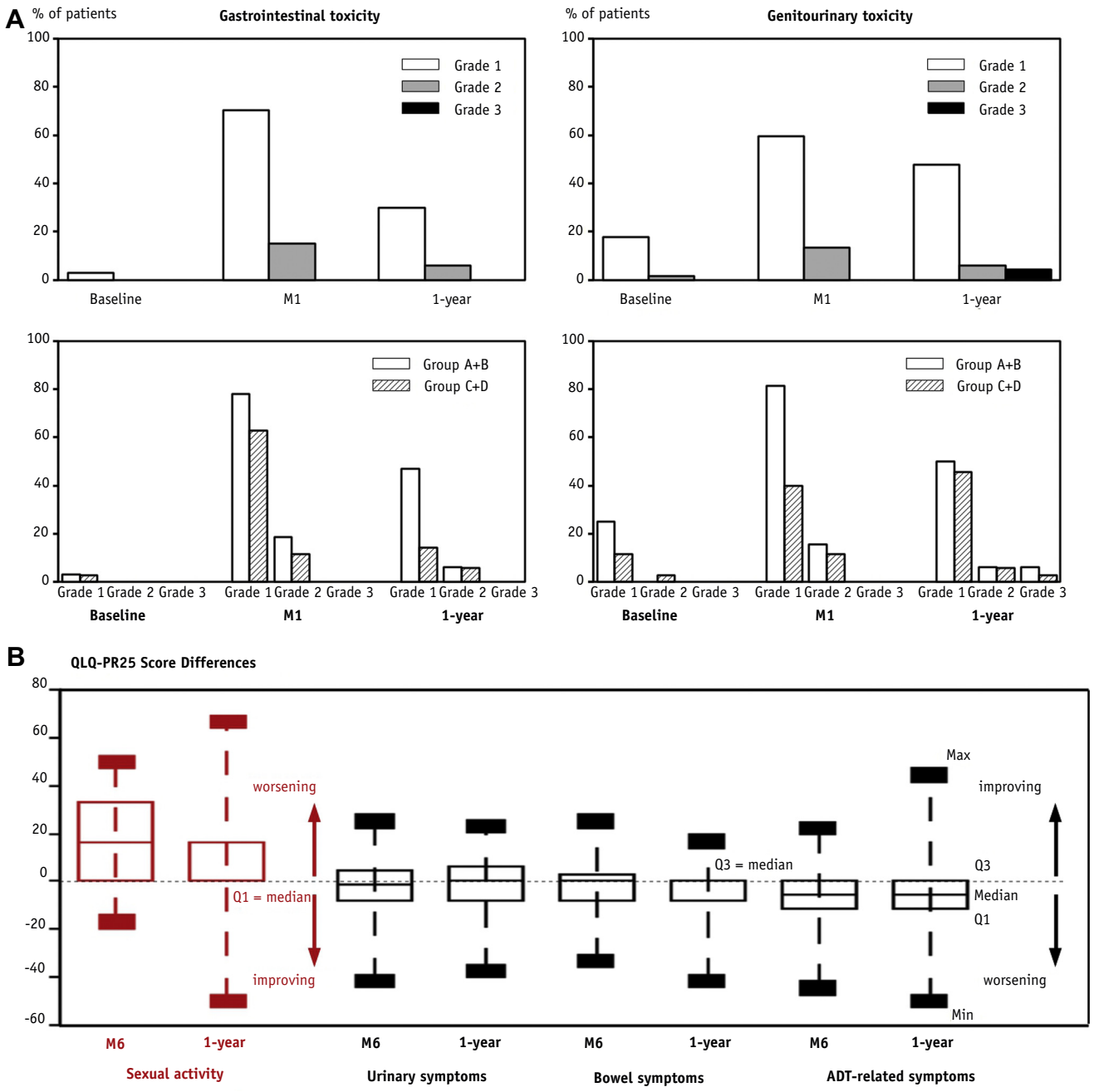

Fig. 3. (A) Number of patients with gastrointestinal (left) and genitourinary (right) Common Terminology Criteria for Adverse Events v4.0 toxic events at M1 (≤1 month after the end of radiation therapy) and 1 year after the end of radiation therapy. The number of patients with urinary and bowel troubles at baseline are given for comparison. Patients in Group A (28 of 67) and Group B (4 of 67) did not receive prior radiation therapy; patients in Group C (29 of 67) and Group D (6 of 67), respectively, received prior prostatic bed and prostate-exclusive radiation therapy. (B) QLQ-PR25 score differences with time. Forty-seven of 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. *Abbreviations:* Max = maximal difference; Min = minimal difference; Q1 = first quartile; Q3 = third quartile.

clinically—significant worsening in sexual activity ($P = .0020$, medium value of +16.6 points) and expected androgen blockade–related symptoms ($P = .0080$, medium value of −5.6 points) was observed.

Discussion

Global tolerance of the BLINDED protocol was satisfactory, in line with retrospective data for high-dose salvage

WPRT in the literature,[12-14] Supplementary Table 3 available online at https://doi.org/10.1016/j.ijrobp.2018.12.020) even in patients with a history of prostatic irradiation.

Based on the measurements of the European Organisation for Research and Treatment of Cancer questionnaires, patient quality of life did not significantly worsen between baseline and 1 year. Sexual activity significantly decreased at 6 months as a result of the androgen blockade—related castration. The increase in dyspnea at 6 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 percent of patients had previous prostate bed or prostate exclusive radiation therapy. Bladder, sigmoid colon, and small bowel ran the risk of being partially reirradiated. There was no increased urinary or digestive toxicity in these patients compared with those who had not previously been irradiated. These results are consistent with those from the other studies that considered pelvic reirradiation using stereotactic body radiation therapy[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 1 year. Further evaluation after a longer follow-up period is required.[18] The limited number of patients also constitutes a weakness.

Conclusions

Rates of acute and 1-year urinary and digestive toxicity after 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 3 BLINDED trial, which will compare these pelvic salvage strategies to long-term androgen blockade, will provide further data on the toxicity of these treatments.

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