Ultra-hypofractionated radiation therapy for unfavourable intermediate-risk and high-risk prostate cancer is safe and effective: 5-year outcomes of a phase II trial

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Objectives

To report toxicity (primary endpoint) and biochemical disease-free survival (BDFS) outcomes of a phase II trial evaluating ultra-hypofractionated radiation therapy (UHRT), focusing on patients with unfavourable intermediate-risk and high-risk prostate cancer (PCa).

Patients and Methods

From 2012 to 2017, 154 patients (92 with unfavourable intermediate-risk or high-risk PCa) were treated with helical TomoTherapy delivering 43.8–45.2 Gy in eight fractions over 3 weeks. Of these, 73% received hormonotherapy (51% neoadjuvant).

Results

The median (range) follow-up was 48 (19–84) months. For the whole series, crude BDFS and 5-year BDFS rates were 97.4% and 94.3%, respectively. The corresponding figures for unfavourable intermediate-risk and high-risk PCa were 96.7% and 90%, respectively. The crude metastasis-free survival rate was 98% for the unfavourable intermediate-risk and high-risk group. For the whole series, the 5-year cumulative urinary/intestinal grade 2+ late toxicity was 17.8/7.4%. No grade 4–5 toxicity was observed. One patient experienced late grade 3 toxicity (urinary).

Conclusion

This eight-fraction UHRT regimen can be safely delivered to patients with unfavourable intermediate-risk/high-risk PCa. Its relapse rates are similar to those reported for the combination of external beam radiotherapy plus brachytherapy, however, the observed toxicity profile is milder. The disease survival rates compare favourably with historical controls in some other forms of radiotherapy, with similar side effects. Since the low rate of biochemical/metastasis relapse is encouraging, further research to confirm these results is justified.

Keywords

stereotactic body radiotherapy, brachytherapy, high risk, hypofractionated radiotherapy, quality of life, #ProstateCancer, #PCSM

Introduction

In the treatment of localized prostate cancer (PCa), the addition of even a low dose of external beam radiotherapy (EBRT) to long-term androgen deprivation therapy (ADT) has been shown to improve overall survival in patients with high-risk PCa compared with ADT alone [1]. Delivering EBRT to 78–80 Gy with a conventionally fractionated scheme additionally provides an advantage with regard to biochemical disease-free survival (BDFS), compared with low-dose EBRT, but with slightly greater toxicity [2,3]. A modest dose escalation up to 84 $Gy_{1.5}$ (equivalent dose at 2 Gy per fraction assuming α/β 1.5 Gy) using moderate hypofractionation (2.5–3.5 Gy/fraction) has shown non-inferior relapse rates compared with conventional fractionation and might improve disease-free survival (DFS) in intermediate-risk PCa [4]. Further dose escalation by combining EBRT and a brachytherapy boost has demonstrated an improvement in biochemical control compared with that attained with 78 Gy EBRT, but at the expense of unacceptable grade 3 urinary toxicity rates [5]. Ultra-hypofractionated radiotherapy (UHRT) regimens exploit the radiobiological advantage thought to be associated with the PCa low α/β ratio, by delivering a high dose per fraction (5–10 Gy) in < 10 fractions, with a dose distribution that closely resembles the distribution associated with high-

dose-rate brachytherapy. The most common UHRT scheme is given in four to five fractions of 7–9 Gy. Recent multi-institutional pooled analyses and meta-analyses have shown advantageous BDFS in patients undergoing UHRT compared to historical controls, with minimal severe toxicity rates for low-risk and intermediate-risk PCa [6,7]. For this group of patients, there is now level 1 evidence demonstrating that seven-fraction UHRT is not inferior to conventional-dose normofractionated radiotherapy [8]. However, there is a lack of data for patients with unfavourable-risk disease; therefore, the role of UHRT in high-risk patients is still controversial [9]. In the present study, Extreme Hypofractionated Radiotherapy for Localized Prostate Cancer (EHRAP), we hypothesized that UHRT (45.2 Gy delivered in eight fractions over 3 weeks) could be safely administered to patients with unfavourable intermediate-risk and high-risk PCa, and could yield favourable DFS rates compared with historical controls. In the present paper, we report the 5-year outcomes of this phase II trial, focused on unfavourable PCa.

Patients and Methods

Patient Eligibility and Follow-up

The study protocol was reviewed by an independent agency of the Ministry of Health (the Spanish Agency of Medicines and Medical Devices, *AEMPS*) and approved by the institutional review board. All patients signed specific informed consent and were aware of the institution's standard radiotherapy treatment, which consisted of 20 fractions of 3.17 Gy, five fractions per week [10]. Patients with locally advanced prostate adenocarcinoma (cT3b) or disseminated disease (cN1 or cM1) were excluded. Distant and lymph node metastases were assessed by abdominopelvic CT and bone scan (mandatory for patients with unfavourable intermediate-risk and high-risk disease). Pelvic MRI was used for T staging in 58 patients (38%), providing additional information for N staging. Men with recent acute urinary obstruction requiring bladder catheter or with a baseline IPSS >19 were also ineligible. The following were not exclusion criteria: prior TURP; adenomectomy; low maximum urinary flow; and large prostate volume.

Patients were categorized according to the National Comprehensive Cancer Network (NCCN) risk classification system, version 4 [11]. Patients were prospectively assessed at baseline, weekly during the treatment, at 2 months, and every 6 months thereafter.

Radiation Treatment

Planning

Planning CT scans (2 mm thick) were performed with empty rectum and urethral catheter to contrast-enhance the bladder.

In 38% of the patients, multiparametric MRI was performed after the diagnosis in order to stage PCa and improve risk stratification.

Intermediate- and high-risk patients were prescribed a dose of 45.2 Gy (92 $EQD_{1.5}$) with 95% planning target volume (PTV) coverage delivered in eight fractions, while for low-risk patients the dose was reduced to 43.84 (87.4 $Gy_{1.5}$). Fractions were administered two to three times per week, Monday to Friday, over 3 weeks. The clinical target volume (CTV) included 3–5 mm of extraprostatic fat in unfavourable intermediate-risk/high-risk patients, depending on the rectal examination, ultrasonography, MRI and biopsy findings (location of Gleason 8–10 adenocarcinoma, periprostatic extension or nodules). For the low-risk/favourable intermediate-risk group the CTV encompassed 1–2 mm around the prostate gland. The CTV also included the proximal 2-cm seminal vesicles along the vertical line for the unfavourable intermediate-risk/high-risk group and 1-cm for favourable intermediate-risk group. PTV margins of 3 mm posteriorly and 5–7 mm in the other dimensions were added to CTV.

Two modifications were made to the treatment protocol in 2015: an endorectal balloon (ERB) filled with 100 mL air was placed to reduce intra-fraction motion and rectal toxicity [12], and the bladder was filled with 200 mL physiological saline solution through a paediatric bladder catheter prior to each treatment fraction. For patients without an ERB, the rectum and bladder were contoured (1 cm above and below the PTV) as solid organs. For patients with an ERB, the rectal and bladder wall (5-mm thickness) was contoured instead. Dose–volume limits for normal tissues are summarized in Table S1.

Treatment

All patients included in the present study were treated with helical TomoTherapy® (Accuray, Sunnyvale, CA, USA). Unlike high-dose-rate brachytherapy or robotic linac, the achieved dose distribution was fairly homogeneous, with doses into the PTV ranging from 95% to 103% of the prescribed dose; therefore, there were no hot spots in the urethra or the prostate gland. As margins were wide, we ensured that ~8–10 mm beyond the prostate capsule received ~90 $Gy_{1.5}$ in intermediate-risk and high-risk patients. Steep dose gradients between the prostate and rectum allowed the sparing of the lateral and posterior rectal mucosa from high doses. Dose distribution on a typical patient without an ERB and with an ERB is shown in Fig. S1. After a cleansing enema, with the patient lying supine on the treatment unit couch, with knees flexed and feet flat, the ERB was placed by the physician at the depth previously determined during the simulation CT, using its marked scale and stopper. The depth of insertion, to position the balloon at the prostate/seminal vesicles in a comfortable and reproducible way, was rather

variable among patients, and therefore had to be individualized. In the treatment position, using a simple positioning device (Combifix; CIVCO, Kalona, IA, USA), a megavoltage CT was acquired every day before treatment. Then, it was co-registered with the simulation CT using CTV and bone anatomy, and finally, the isodose curves displayed to assist with the online correction of both the prostate-seminal vesicles inter-fraction shift and the ERB position, if necessary (Fig. S2). Online corrections over 3 mm were uncommon (<5% of the total treatment fractions). Prophylactic α-blockers (tamsulosin 0.4 mg/day) or anti-inflammatory medications (hydrocortisone enema, given a few millilitres once a day) were routinely administered during radiotherapy. Treatment was completed over a period of 13–23 days in 95% of the patients. ADT was prescribed for 6 months in favourable intermediate-risk/unfavourable intermediate-risk patients. It consisted of 1 month of bicalutamide 50 mg/day with one 6-month injection of leuprolide or triptorelin, ~3 months before radiotherapy. For high-risk patients ADT continued with 6-month injections up to 24 months.

Study Endpoints

Toxicity

Baseline urinary and intestinal symptoms were recorded before the start of the radiotherapy. Physician-reported toxicities were defined using Common Terminology Criteria for Adverse Events (CTCAE) version 3. Patient-reported urinary toxicity was assessed with the IPSS. The minimal important difference (MID) or minimal clinically important difference is the smallest change in a treatment outcome that an individual patient would perceive as clinically meaningful. For IPSS, the MID threshold was defined as the mean IPSS value at baseline plus 0.5 standard deviation of the series. Side effects occurring within 2 months of radiotherapy treatment were categorized as acute toxicities, and those developing after 2 months were considered late toxicities. We also aimed to identify potential clinical predictors of genitourinary (GU) and gastrointestinal (GI) toxicities among the following: age; Charlson index; diabetes; hypertension; coronary artery disease; intake of anticoagulants/antiplatelet drugs; intake of α-1-blocker for symptomatic BPH; placement of bladder catheter before every radiotherapy fraction; history of adenomectomy/TURP; baseline IPSS (1–7 vs 8–19); baseline IPSS (irritative subscore, questions 2, 4, 7); baseline IPSS (obstructive subscore, questions 1, 3, 5, 6); baseline IPSS (question 3); placement of ERB; history of symptomatic haemorrhoids; ADT, radiotherapy dose (43.84 Gy vs 45.20 Gy); NCCN risk group; and year of radiotherapy treatment (2012–2014 vs 2015–2017). Late toxicity after radiotherapy, as a consequential late damage of acute toxicity, was also investigated.

Quality of Life

Quality of life was assessed using the Expanded Prostate Cancer Index Composite (EPIC)-26 questionnaire at baseline, 2 months after radiotherapy, then every 6 months for 3 years, and every year thereafter. For each domain, an MID threshold was defined as the mean EPIC score at baseline plus 0.5 standard deviation of the series. The impact of UHRT on quality of life will be extensively addressed in another publication.

Disease-Free Survival

Failure was defined as biochemical recurrence or the administration of any salvage, antiandrogen, or systemic PCa therapy. An increase in PSA level of 2 ng/mL above the prior nadir was scored as a biochemical failure, unless followed by a decline to a new nadir. Patients who developed biochemical recurrence underwent either bone scan and CT or body MRI every 6 months.

Study Objectives and Statistics

The primary objective of this prospective study was safety, i.e. to determine whether the 5-year incidence of patients experiencing CTCAE grade 3 or higher toxicities exceeded 10%, a rate deemed excessive [13]. A sample size of 100 patients yielded 90% power for identifying an excessive toxicity rate at the one-sided 5% significance level. Accounting for unevaluable patients, the minimal planned enrolment was 120 patients.

The secondary objective was efficacy, i.e. to determine whether, for unfavourable intermediate-risk and high-risk patients, UHRT improved 5-year DFS from an expected rate of 75%, the average rate reported with ADT plus either dose-escalated normofractionated EBRT [14,15] or EBRT with brachytherapy studies [16]. Potential prognostic factors of GU or GI toxicity were assessed using a bivariate Cox proportional hazard model. Variables with a P value < 0.2 were included in a multivariate Cox proportional hazard model. A P value of <0.05 was considered statistically significant.

Results

Between May 2012 and October 2017, a total of 154 patients were treated, 92 of whom had unfavourable intermediate-risk or high-risk PCa. Patient characteristics are listed in Table 1. A total of 112 patients (73%) received ADT. Seventy-nine men received neoadjuvant-concomitant ADT over the course of 6 months. Thirty-three continued the ADT (6-month injections) up to 24 months. The median (range) follow-up of the series was 48 (19–84) months. At the time of analysis, nine patients (5.7%) were no longer being followed up: seven died, and two were lost to follow-up. One death may be

Table 1 Patient, tumour and dosimetry characteristics.

Characteristic	Entire series (N = 154)	Unfavourable intermediate-risk and high-risk group (N = 92)
Age, years		
Median (range)	72 (50–81)	73 (50–81)
Clinical stage, n (%)		
T1c	56 (36)	17 (19)
T2a	21 (14)	9 (10)
T2b	26 (17)	20 (22)
T2c	19 (12)	14 (15)
T3a	30 (20)	30 (33)
Tx	2 (1)	2 (1)
Gleason score, n (%)		
3 + 3	64 (42)	15 (16)
3 + 4	38 (25)	25 (27)
4 + 3	24 (15)	24 (26)
4 + 4	20 (13)	20 (23)
4 + 5	5 (3)	5 (5)
5 + 4	3 (2)	3 (3)
Initial PSA, ng/mL		
Median (range)	9 (1.2–214)	13.5 (4.2–214)
<10	84 (55)	32 (35)
10–20	53 (34)	43 (47)
>20	17 (11)	17 (18)
NCCN risk group, n (%)		
Low-risk	28 (18)	
Favourable intermediate-risk	34 (22)	
Unfavourable intermediate-risk	35 (23)	
Favourable high-risk	37 (24)	
Unfavourable high-risk	20 (13)	
ADT, n (%)		
No	42 (27)	8 (9)
Neo-con	79 (51)	53 (57)
Neo-con-adj	33 (22)	31 (34)
ERB, n (%)	75 (49)	49 (53)
Dosimetry		
CTV, %		
D98%	100.1	
PTV, %		
D98%	98.1	
D2%	102.1	
Rectal wall, %		
V100%	5.2	
V90%	15.1	
V80%	19.8	
Bladder wall, %		
V100%	7	
V90%	11.4	
V50%	25.5	
Median volumes, cm³		
CTV	64.8	
PTV	118.7	
Rectal wall	23.4	
Bladder wall	43.7	

ADT, androgen deprivation therapy; CTV, clinical target volume; D2% (near maximum), percent of the prescribed dose covering 2% of the target volume; D98% (near minimum), percent of the prescribed dose covering 98% of the target volume; ERB, endorectal balloon; NCCN, National Comprehensive Cancer Network; Neo-con, Neoadjuvant-Concomitant; Neo-con-adj, Neoadjuvant-Concomitant-Adjuvant; PTV, planning target volume; Vn%, percentage of the organ-at-risk covered by n% of the prescribed dose.

linked to PCa, while the others were attributable to causes unrelated to either PCa or the treatment (four related to second tumours, one suicide, one congestive heart failure).

Relapse occurred in four patients for the entire series (97.4% crude BDFS) and three for the unfavourable intermediate-risk/high-risk group (96.7% crude BDFS). All had a PSA increase >2 ng/mL over PSA nadir. No local recurrence of the PCa was detected after performing bi-parametric MRI and rectal examination. Pelvic lymph node and distant metastases were observed in one patient. Bone metastases were documented in three patients: two in the high-risk group and one in the favourable intermediate-risk group, giving a crude metastasis-free survival rate of 98%. Actuarial DFS plots are shown in Fig. 1. For the entire series, the actuarial 5-year DFS rate was 94.3%. For the unfavourable intermediate-risk/high-risk PCa group, the estimated 5-year DFS rate was 90%, which proved to be superior to the 75% historical control rate we chose for comparison with other forms of EBRT [14,15]. For unfavourable intermediate-risk/high-risk patients the 5-year cumulative incidence of metastasis was 2.7% (Fig. 2). The crude metastasis-free survival rate was 98%.

Figure 3 provides a summary of the observed toxicities for the whole series. No grade 4 or 5 toxicities occurred. No patient reported acute grade 3 side effects. One patient experienced late grade 3 dysuria 9 months after radiotherapy as a result of a urethral ulcer that resolved within 3 months. It required a suprapubic bladder tap and pregabalin. The mean IPSS returned to baseline between 2 and 6 months after radiotherapy (Fig. 3). There was no late grade 3 intestinal toxicity. The incidence of grade 2/3 GU and GI toxicities at 3 years was 1.4/0% and 0/0%, respectively. Kaplan–Meier 5-year cumulative Grade 2–3 GU and GI toxicities were 17.8% and 7.4%, respectively (Fig. S3). These treatment-related side effects were far below the 10% grade 3–5 toxicity rate deemed excessive [13].

The 17 variables potentially correlated with acute or late urinary toxicity, and the 12 variables potentially correlated with acute or late intestinal toxicity are listed in Table 2. P values for all variables after univariate analysis are displayed. Those with P values > 0.2 were included in the multivariate analysis. P values, hazard ratios and CIs for those variables are also shown in Table 2. Multivariable analysis showed that the placement of a urethral catheter was significantly associated with increased acute GU toxicity, whereas hypertension and history of α-1-blocker intake for symptomatic BPH were significant variables predicting for late GU toxicity. None of the prognostic factors investigated were found to be predictive of acute GI toxicity. Ischaemic cardiopathy might be correlated with higher incidence of late GI morbidity.

The mean EPIC urinary irritative/obstructive subdomain score exhibited transient statistically significant declines at 2 months after radiotherapy that barely reached the MID. It subsequently returned to baseline at 6 months and continued

Fig. 1 Actuarial survival plots: disease-free survival in the entire series (**A**) and in the unfavourable intermediate-risk/high-risk group (**B**).

A

Months	RT	12	24	36	48	60	72
Patients (n)	154	149	124	97	71	52	11

B

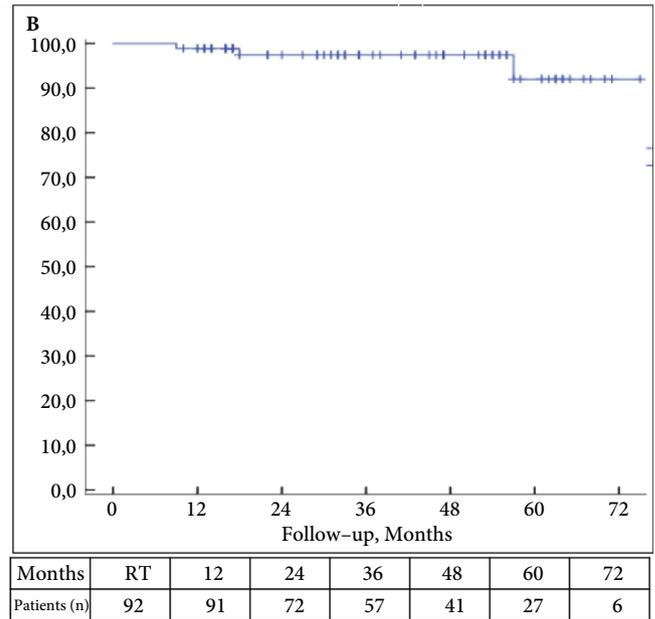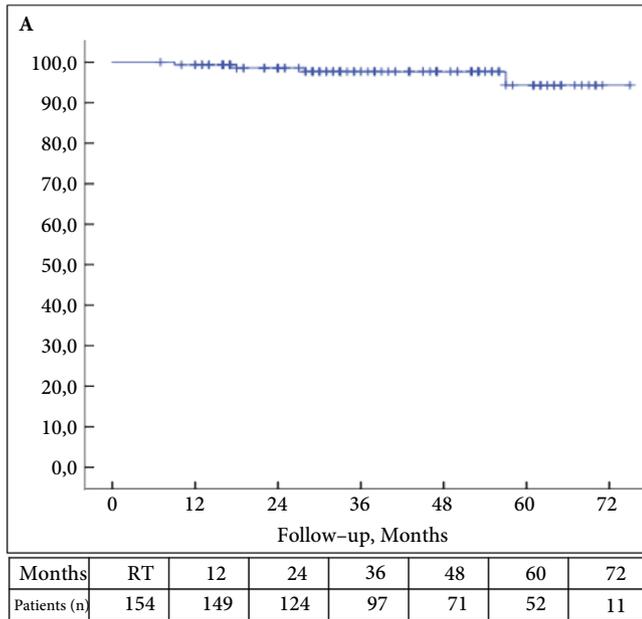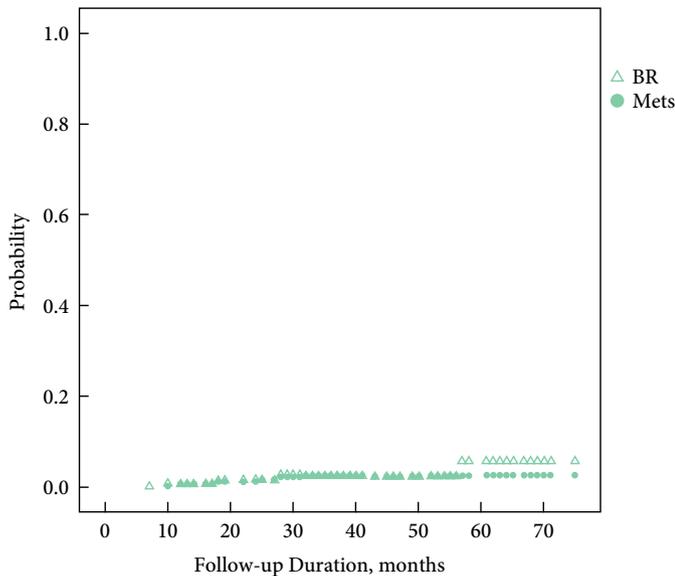| Months	RT	12	24	36	48	60	72
Patients (n)	92	91	72	57	41	27	6

Fig. 2 Cumulative incidence of biochemical recurrence (BR) and distant metastasis (Mets).

to be around the baseline level thereafter (Fig. 4). UHRT had no impact on the urinary incontinence subdomain.

Discussion

A meta-analysis published this year, including more than 6000 patients, stated that UHRT had sufficient evidence to be supported as a standard treatment option for localized PCa [7]. It also highlighted that only few UHRT studies included patients with high-risk PCa, and those that did only had a very small proportion of such patients. Additionally, most studies including high-risk patients did not separately report outcomes by risk group; therefore, there is a lack of data from phase II/prospective trials on unfavourable PCa treated with UHRT. The present study (ISRCTN19419439) shows that UHRT for unfavourable intermediate-risk and high-risk PCa could be safely undertaken by experienced institutions, provided that planning and delivery requirements were fulfilled. Prescribing 92 $Gy_{1.5}$ (delivered in eight fractions of 11.5 $Gy_{1.5}$) over 3 weeks resulted in very low rates of 5-year severe toxicity (grade 3+). Relapse rates were similar to dose escalation combining brachytherapy and EBRT, and compared favourably with historical controls of other forms of radiotherapy.

As our objective was to improve BDFS without increasing toxicity, our treatment schedule was designed to be equi-effective for late normal tissue toxicity probability with our standard radiotherapy treatment (20 fractions of 3.17 Gy) under the linear quadratic model, i.e. 78 Gy_3 (intermediate-risk and high-risk patients) or 74 Gy_3 (low-risk patients), while escalating radiation dose as close as possible to 100 $Gy_{1.5}$ to PCa cells. Using EBRT exclusively, that objective could only be achieved through extreme hypofractionation. In order to diminish the intra-fraction shift associated with the irradiation time, even using an ERB [17], dose per fraction had to be delivered, fulfilling demanding dosimetric criteria, in a treatment time that we considered acceptable, i.e. <10 min. As a result of the previous considerations, our radiotherapy schedule consisted of eight fractions of 5.65 Gy prescribed to 95% of the PTV. Following the

Fig. 3 Toxicity event rates by time point. Grade distribution of (**A**) genitourinary (GU) and (**B**) gastrointestinal (GI) toxicity, measured by the Common Terminology Criteria for Adverse Events. (**C**) Patient-reported problems. Chronological changes of IPSS in the whole series. Higher scores indicate more urinary symptoms. Mean IPSS values significantly increased during and after radiotherapy, returning to initial levels between 2 and 6 months thereafter. The asterisk represents a score that was statistically different ($P < 0.05$, *t*-test) from the baseline value. B, at baseline; E Rt, at the last fraction of radiotherapy; MID, minimal important difference.
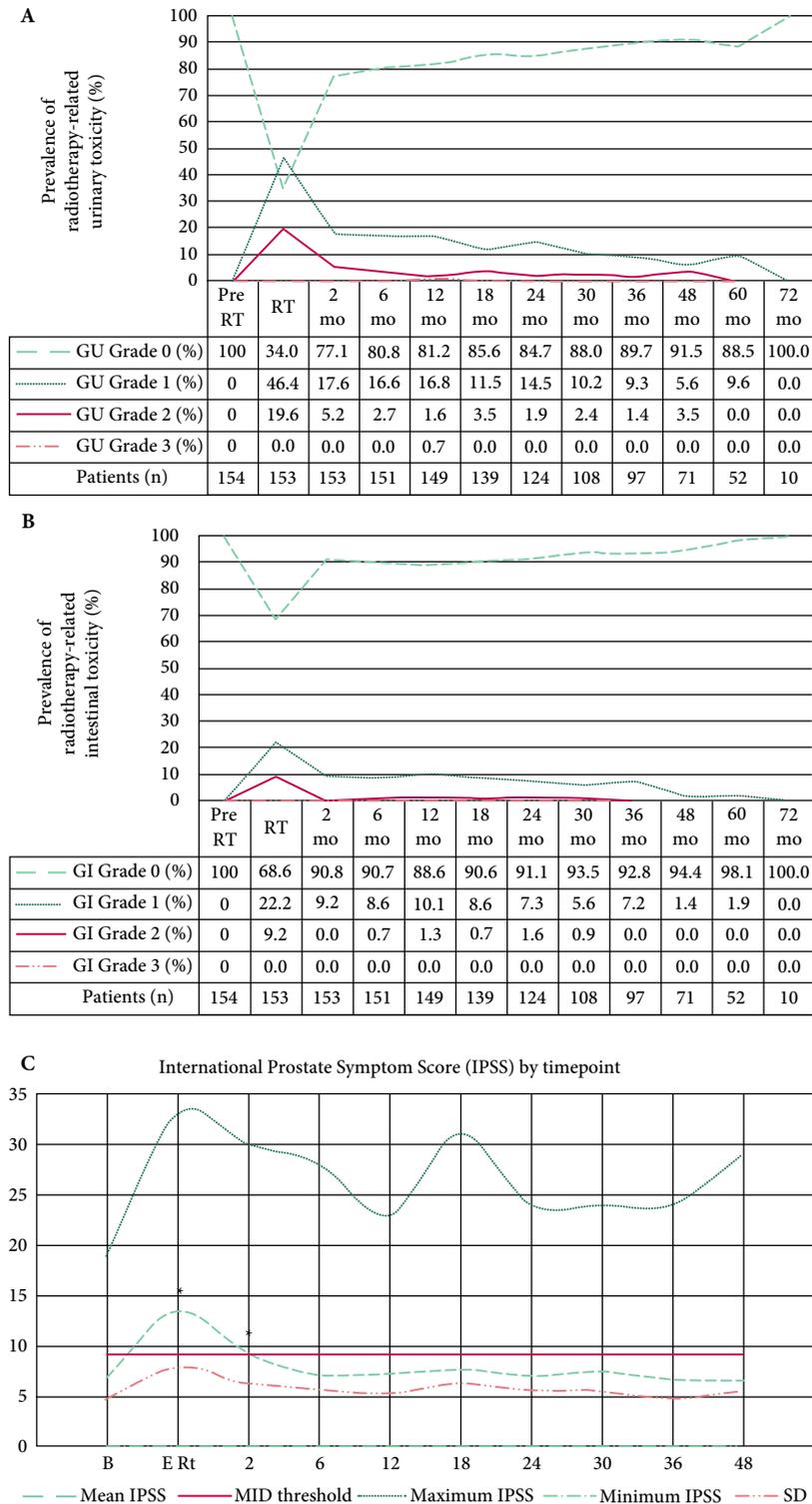
A

	Pre RT	RT	2 mo	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	48 mo	60 mo	72 mo
GU Grade 0 (%)	100	34.0	77.1	80.8	81.2	85.6	84.7	88.0	89.7	91.5	88.5	100.0
GU Grade 1 (%)	0	46.4	17.6	16.6	16.8	11.5	14.5	10.2	9.3	5.6	9.6	0.0
GU Grade 2 (%)	0	19.6	5.2	2.7	1.6	3.5	1.9	2.4	1.4	3.5	0.0	0.0
GU Grade 3 (%)	0	0.0	0.0	0.0	0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Patients (n)	154	153	153	151	149	139	124	108	97	71	52	10

B

	Pre RT	RT	2 mo	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	48 mo	60 mo	72 mo
GI Grade 0 (%)	100	68.6	90.8	90.7	88.6	90.6	91.1	93.5	92.8	94.4	98.1	100.0
GI Grade 1 (%)	0	22.2	9.2	8.6	10.1	8.6	7.3	5.6	7.2	1.4	1.9	0.0
GI Grade 2 (%)	0	9.2	0.0	0.7	1.3	0.7	1.6	0.9	0.0	0.0	0.0	0.0
GI Grade 3 (%)	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Patients (n)	154	153	153	151	149	139	124	108	97	71	52	10

C International Prostate Symptom Score (IPSS) by timepoint

Table 2 Predictors for the incidence of genitourinary and gastrointestinal grade ≥1 toxicities

	Univariate analysis P	Multivariate analysis	
		P	Hazard ratio (CI)
Acute GU toxicity predictors			
Age (≤72 vs >72 years)	0.733		
Charlson index	0.469		
Diabetes	0.925		
Hypertension	0.777		
Cardiopathy	0.623		
History of α-1 blocker intake	0.632		
Anti-aggregant/anticoagulant	0.115	0.840	0.751 (0.490; 1.175)
TURP/adenomectomy	0.349		
ADT	0.592		
Bladder catheter	0.005	0.008	1.742 (1.157; 2.662)
Dose (43.8 vs 45.2 Gy)	0.549		
Baseline IPSS (<8 vs ≥8)	0.544		
Baseline IPSS (irritative)	0.770		
Baseline IPSS (obstructive)	0.440		
Baseline IPSS (question 3)	0.640		
NCCN risk group	0.929		
Year of the radiotherapy	0.011	0.210	0.966 (0.650;1.431)
Late GU toxicity predictors			
Age (≤ 72 vs >72 years)	0.249		
Charlson index	0.365		
Diabetes	0.676		
Hypertension	0.036	0.030	2.041 (1.072; 3.887)
Cardiopathy	0.843		
History of α-1 blocker intake	0.024	0.030	2.110 (1.072; 4.151)
Anti-aggregant/anticoagulant	0.529		
TURP/adenomectomy	0.061	0.197	0.720 (1.072; 4.917)
ADT	0.139	0.458	1.342 (0.616; 2.924)
Bladder catheter	0.018	0.333	1.610 (0.614; 4.218)
Dose (43.8 vs 45.2 Gy)	0.156	0.216	1.805 (0.708; 4.599)
Baseline IPSS (<8 vs ≥8)	0.144	0.548	1.211 (0.649; 2.262)
NCCN risk group	0.610		
Year of radiotherapy	0.002	0.005	3.857 (1.501; 9.912)
Acute GI toxicity predictors			
Age (≤72 vs >72 years)	0.469		
Charlson index	0.887		
Diabetes	0.887		
Hypertension	0.759		
Cardiopathy	0.520		
Placement of ERB	0.000	0.082	0.365 (0.118; 1.135)
Anti-aggregant/anticoagulant	0.996		
Haemorrhoids	0.210		
ADT	0.546		
Dose (43.8 vs 45.2 Gy)	0.252		
NCCN risk group	0.424		
Year of the radiotherapy	0.000	0.275	1.788 (0.630; 5.079)
Late GI toxicity predictors			
Age (≤72 vs >72 years)	0.477		
Charlson index	0.368		
Diabetes	0.365		
Hypertension	0.361		
Cardiopathy	0.099	0.000	
Placement of ERB	0.000	0.158	3.222 (0.636; 16.328)
Anti-aggregant/anticoagulant	0.449		
Haemorrhoids	0.128	0.317	0.606 (0.227; 1.616)
ADT	0.422		
Dose (43.8 vs 45.2 Gy)	0.342		
NCCN risk group	0.002	0.162	
Year of radiotherapy	0.000	0.214	2.902 (0.540; 15.587)

ADT, androgen deprivation therapy; ERB, endorectal balloon; GI, gastrointestinal; GU, genitourinary; NCCN, National Comprehensive Cancer Network.

recommendations of Fowler et al. [18] for avoiding excessive short overall times, fractions were planned to be administered two (Monday and Thursday) or three times (every other day) per week over 2.5–3 weeks instead of daily fractions over 1.5 weeks. ASTRO-ASCO-AUA evidence-based UHRT guidelines suggest that avoiding consecutive daily treatments could decrease toxicity [19]. The HYPO-RT-PC phase III trial has also found that, probably due to the shorter overall treatment time, early side effects were more pronounced with ultra-hypofractionation than with conventional fractionation [8]. Finally, there is level 1 evidence that five-fraction UHRT delivered once per week improves acute urinary and intestinal quality of life compared with every-other-day delivery [20]. By contrast, repopulation of PCa and how the 'time factor' might affect tumour control is currently unknown, especially for high-grade tumours [21,22]. Also, in light of the discouraging results obtained after single-dose high-dose-rate brachytherapy [23] for low- to intermediate-risk PCa we should be cautious when designing clinical trials for unfavourable PCa with few fractions (< 5) or for an overall treatment time < 7 days.

For low-risk and favourable intermediate-risk patients, this trial represents a considerable effective biological dose escalation (87 Gy$_{1.5}$) over typical 76–78 Gy-(IMRT) intensity-modulated radiation therapy. The 5-year BDFS rate of 97.9% observed in the present trial, EHRAP, was similar to the 5-year BDFS rates of 90–95% reported with dose-escalated 86 Gy-IMRT [14], low-dose-rate brachytherapy [24], and UHRT [7]. For this group of patients, any EBRT treatment delivering a dose up to 80–85 Gy$_{1.5}$ (e.g. moderate hypofractionated EBRT, UHRT in five fractions of 7 Gy), or brachytherapy alone obtains excellent DFS outcomes with low toxicity rates.

To set in context the outcomes of the present trial, we gathered the data on BDFS rates and grade 3+ toxicity of several trials [5,7,8,25–30] with a minimum 5-year follow-up (Fig. 5).

Further information on these studies is summarized in Table S2.

For unfavourable intermediate-risk and high-risk patients, the 5-year BDFS rate of 90% observed in EHRAP compares favourably with the 70–80% rate observed in the 86 Gy-IMRT group of the Memorial Sloan Kettering Cancer Centre (MSKCC) [14] and the 70% rate reported in the 78 Gy-arm of the Radiation Therapy Oncology Group (RTOG) 9406 [15]. Our results are similar to the 92% 5-year BDFS rate observed in Jackson's meta-analysis for intermediate-risk patients [7], and also comparable with the 89% 5-year BDFS rate reported in the ASCENDE-RT trial for the combined pelvic EBRT + brachytherapy + ADT arm [27], but without the high grade 3 toxicity rates observed in the latter trial.

Fig. 4 Patient-reported problems. Mean Expanded Prostate Cancer Index Composite (EPIC) scores in the whole series. Higher values indicate better quality of life. EPIC irritative/obstructive subdomain: compared with baseline the value significantly decreased at 2 months after radiotherapy (asterisk), scarcely reaching clinical importance. EPIC incontinence subdomain: radiotherapy does not affect the mean incontinence score. MID, minimal important difference.
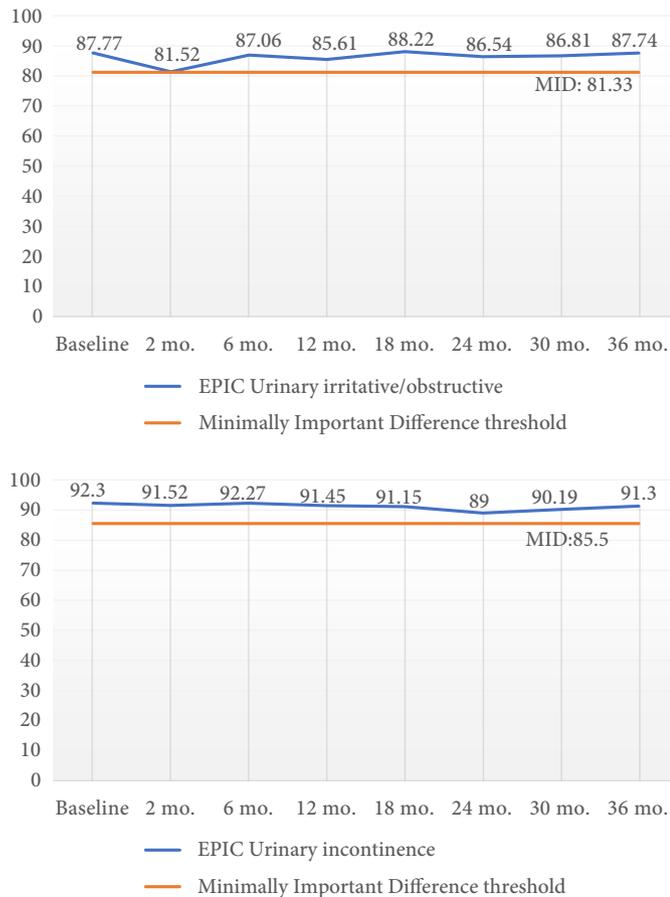

Other trials treating patients with EBRT plus brachytherapy boost plus ADT resulted in 5-year BDFS rates of 75–86% [31,32]. As mentioned previously, the HYPO-RT-PC phase III trial demonstrated that UHRT regimens are not inferior to conventionally fractionated 78-Gy EBRT for intermediate-risk patients [8]. This trial also included a group of selected 62 high-risk patients (maximum PSA allowed was 20 ng/mL), although the tumour control rates for this specific group were not reported. Their fractionation scheme was very similar to ours, delivering seven fractions of 6.1 Gy over 2.5 weeks, which, like the present study, is equivalent to 92 $Gy_{1.5}$. The main differences between HYPO-RT-PC and EHRAP are: (1) HYPO-RT uses three-dimensional conformal radiotherapy in 80% of patients with two-dimensional image guidance with intraprostatic fiducials vs helical tomotherapy with three-dimensional image guidance and an ERB in EHRAP; (2) seminal vesicles were not included in the volume target in HYPO-RT vs at least 2 cm of seminal vesicles in all patients

in EHRAP; and (3) HYPO-RT did not allow ADT vs 91% of unfavourable intermediate-risk-high-risk patients receiving ADT in EHRAP. Recently, a randomized phase II trial compared five different UHRT and moderate hypofractionated schedules. At a median follow-up of 7.5 years, the results suggested that the efficacy of the 10-fraction arm and the 15/20-fraction arm was superior to the five-fraction arm, with no differences in late toxicity among groups [33]. Based on these outcomes and the favourable tumour control results obtained by HYPO-RT-PC and EHRAP, UHRT schemes delivering 6–10 fractions should also be included in future phase III trials involving unfavourable intermediate-risk and high-risk PCa.

One may speculate whether increasing the radiotherapy dose close to 100 $Gy_{1.5}$ was the main factor responsible for the high DFS rates observed in this trial. Another hypothesis is that the addition of ADT, even delivering such a high total dose, might have played a crucial role in the unfavourable intermediate-risk/high-risk patients. A multi-institutional consortium study reported a 93% 5-year BDFS rate in the unfavourable intermediate-risk subgroup using UHRT alone [6], suggesting very high dose delivered with UHRT or through a brachytherapy boost may obviate ADT in this group of patients. However, a recent meta-analyses of randomized trials addressing the role of ADT with dose escalation using a brachytherapy boost concluded that the addition of ADT to the brachytherapy boost further improved metastases free- and overall survival by 20–30% [34]. Two-year adjuvant ADT added to the conventional radiotherapy dose (76–82 Gy) improved BDFS and overall survival compared with short-term ADT in high-risk patients [35]. To date, there are no published studies addressing the efficacy of long-term ADT in combination with dose escalation to > 85 $Gy_{1.5}$ in high-risk patients. For unfavourable PCa, in the absence of a randomized trial showing otherwise, dose escalation with brachytherapy or UHRT, should not replace ADT.

The toxicity of prostate UHRT relative to the combination of EBRT plus brachytherapy or other forms of moderate hypofractionated or conventional fractionated EBRT has been the subject of debate [5,36,37]. Figure 5 shows that late grade 2–5 toxicities in the present study were similar to those from centres using five-fraction UHRT and compare favourably with other radiation therapies. In particular, we did not observe the high incidence of late urinary grade 3 toxicities associated with the combination of EBRT and brachytherapy. As a small percentage of late toxicities may develop beyond 5 years, the current toxicity rates we are presenting are unlikely to largely underestimate actual long-term rates. For example, in the RTOG 9805 study, the rate of grade 2–5 GU toxicities increased < 3% between 5 and 9 years after low-dose-rate brachytherapy [38]. The present trial delivered a significant dose escalation, protracted overall treatment time, used three-dimensional image guidance before every treatment

Fig. 5 Comparative rates of biochemical disease-free survival (BDFS) and grade 3+ late toxicity across various radiotherapy modalities. BT, interstitial brachytherapy; EBRT, external beam radiotherapy; GI, gastrointestinal; GU, genitourinary; HDR high-dose-rate; HR, high-risk; IR, intermediate risk; UHRT, ultra-hypofractionated radiotherapy.
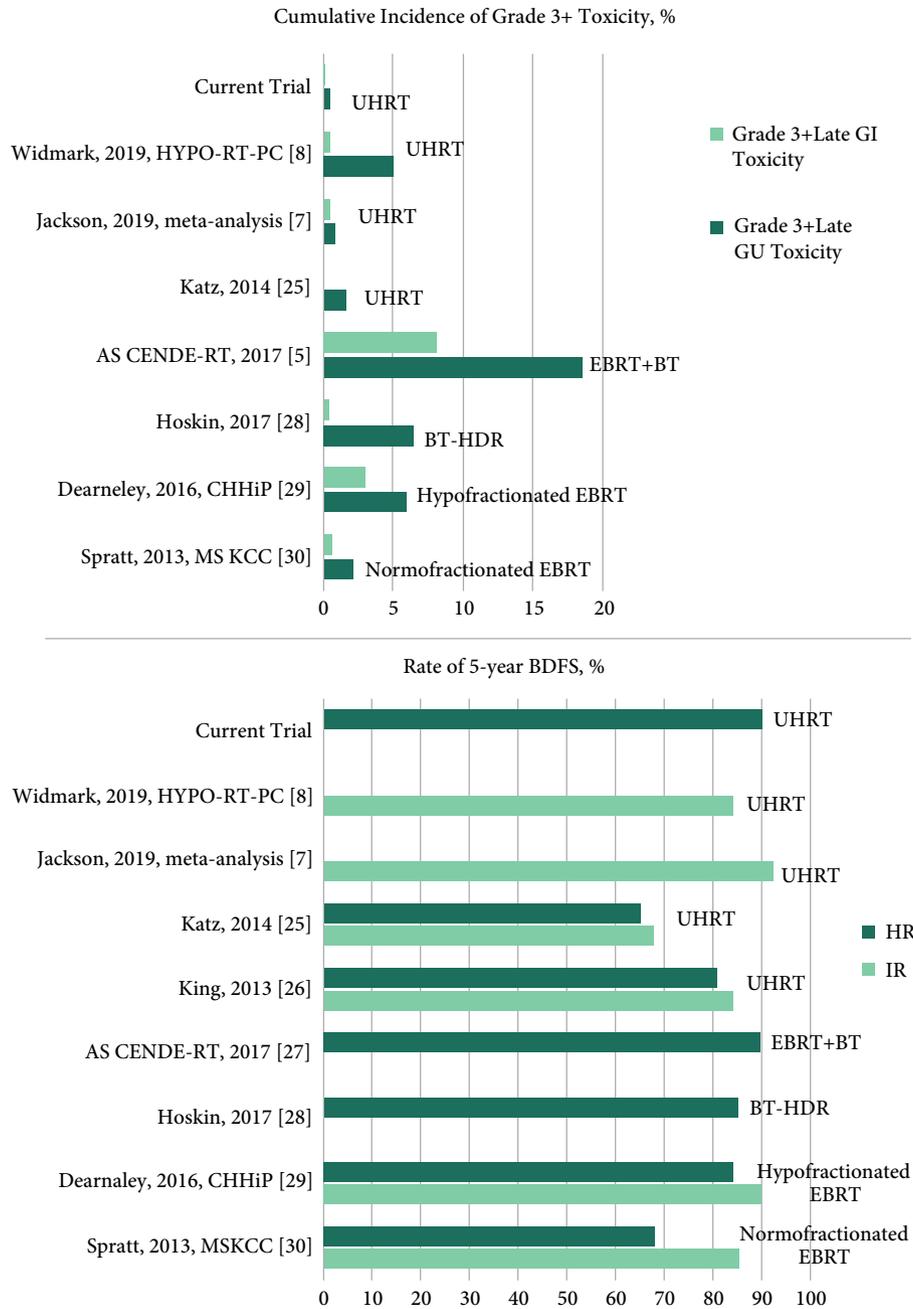
fraction, avoided hot spots into the prostate gland, urethra and rectal mucosa, placed an ERB in half of the patients, and followed rigid constraints of dose to normal tissues. The rigorous control of these factors may account for the favourable late toxicity rates observed in the present study. It has been described that patients who develop acute grade 2+ urinary or intestinal symptoms during treatment experience higher incidence of late toxicity [13]. To reduce the probability

of late grade 2+ intestinal toxicity as a consequential effect of acute rectal injury [39], a corticosteroid enema was administered every night during the radiotherapy treatment with the purpose of preventing acute rectitis. Prophylactic treatment with topical rectal corticosteroids during radiotherapy significantly reduced the risk of rectal bleeding and radiation-induced mucosal changes and improved patient's quality of life in a randomized clinical trial [40].

Reaching a median follow-up > 5 years is required for determining actual long-term rates of DFS, as BDFS might significantly drop after 4–5 years [27]. Further follow-up is guaranteed.

In the present trial, a dose of 92 $Gy_{1.5}$ was delivered in eight fractions over 3 weeks to ~98% of a large PTV that included > 5 mm beyond the prostate capsule and half of seminal vesicles. The 5-year BDFS rate of 90%, observed in this series of unfavourable intermediate-risk/high-risk patients, is a figure which is not surpassed by other radiotherapy techniques. The toxicity profile was very favourable and the impact on urinary quality of life minimal and transient. Further studies should define the most effective fractionation for unfavourable intermediate-risk/high-risk PCa, which should be compared with other curative treatments for localized PCa. The role of ADT along with very high radiotherapy dose also needs to be investigated.

Acknowledgements

Conflict of Interest

Dr. Macias reports grants from Castilla-Leon Public Health Service, during the conduct of the study; and in 2018 I taught for free a webinar organized by Accuray based on an oral communication accepted in ASTRO 2018. Dr. Barrera Mellado has nothing to disclose.

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Abbreviations: ADT, androgen deprivation therapy; BDFS, biochemical disease-free survival; CTCAE, Common Terminology Criteria for Adverse Events; CTV, clinical target volume; DFS, disease-free survival; EBRT, external beam radiotherapy; EHRAP, Extreme Hypofractionated Radiotherapy for Localized Prostate Cancer; EPIC, Expanded Prostate Cancer Index Composite; ERB, endorectal balloon; GI, gastrointestinal; GU, genitourinary; MID, minimal important difference; NCCN, National Comprehensive Cancer Network; PCa, prostate cancer; PTV, planning target volume; RTOG, Radiation Therapy Oncology Group; UHRT, ultra-hypofractionated radiation therapy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Dose distribution on a typical patient without endorectal balloon (A) and with endorectal balloon (B). D $Gy_{1.5}$ = equivalent dose at 2 Gy/fraction assuming a/b 1.5 Gy; D Gy_3 = equivalent dose at 2 Gy/fraction assuming a/b 3 Gy; CTV = clinical target volume; PTV = planning target volume; % iso = isodose curve expressed as a percentage of the prescribed dose.

Figure S2. Example of on-line image-guided tomotherapy on a typical patient with endorectal balloon. Planning CT (grey) and daily megavoltage CT (green) used for position verification show a good correlation for endorectal balloon and clinical target volume coverage (95% isodose in red).

Figure S3. Physician-recorded side effects. Cumulative incidence of urinary and intestinal grade 2+ late toxicity in the whole series.

Table S1. Main dose limits used for target volumes and organs-at-risk.

Table S2. Selected series of unfavorable prostate cancer patients treated with UHRT, hypofractionated EBRT, normofractionated EBRT, brachytherapy, and combination of EBRT and brachytherapy.