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ORIGINAL ARTICLE

Comparative radiobiological analysis and preliminary results of Ultra hypofractionated accelerated radiotherapy for low-risk prostate cancer patients

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Summary

Purpose: *Moderately accelerated hypofractionation (HypoAR) has been recently established as a standard radiotherapy scheme for low-risk prostate cancer. The application of ultra-hypofractionated regimens (ultra-HypoAR), with fraction size above 5 Gy, is also widely tested.*

Methods: *We applied Image Guided Radiation Therapy (IGRT) ultra-HypoAR delivered with Volumetric Modulated Arc Therapy (VMAT) technique in low-risk prostate cancer patients (5.75 Gy/fraction, 40.25 Gy total dose, two fractions per week). A comparative radiobiological analysis of Dose-Volume Histograms (DVH) obtained for target volumes and organs at risk was performed, investigating the advantages and disadvantages of ultra-HypoAR and conventional radiotherapy regimens (CRT). Early clinical results on efficacy and toxicity are also reported.*

Results: *We calculated the Normalized Total Dose (NTD) and NTD with time correction (NTD_T)-based biological Dose- Volume Histograms (bDVH) for bladder and rectum tissue late effects (α/β=4 Gy) and early effects (α/β=10 Gy). Ultra-HypoAR produced a significantly lower biological dose burden than CRT, for both early and late responding tissue components of the bladder and rectum, whether calculated for time-correction or not ($p<0.0001$). Our clinical experience showed that the ultra-HypoAR regimen produced minimal early and late radiation sequelae. The median PSA levels dropped from 9.1 to 0.75 and 0.45 ng/ml at 6 and 12 months, respectively, after the end of therapy.*

Conclusions: *In conclusion, radiobiological analysis of DVHs and preliminary clinical experience predict a better efficacy and low early and late toxicity profile for the tested seven-fraction VMAT ultra-HypoAR regimen with IGRT.*

Key words: *hypofractionation, prostate cancer, radiobiology, radiotherapy, ultra hypofractionation*

Introduction

External beam radiation therapy (EBRT) is widely applied for the treatment of prostate cancer. New techniques like Image Guided Radiation Therapy (IGRT) and Intensity Modulated Radiation Therapy (IMRT) are routinely used aiming to improve the accurate delivery of dose escalated radiation therapy [1]. While conventionally fractionated radiotherapy with 2 Gy dose per fraction is the treatment of choice, continuously accumulating radiobiological and clinical evidence supports the choice of accelerated hypofractionation (HypoAR) [2].

Although concerns have been raised regarding the late tissue toxicity of hypofractionated radiotherapy, the low prostate cancer α/β-ratio value of less than 2 Gy [3,4] strongly supports the efficacy

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of such regimens, when applied with modern techniques that minimize the exposure of normal tissue to radiation. Indeed, the recent radiotherapy guidelines for early-stage prostate cancer reported by ASTRO/ASCO/AUA adopt the choice of moderately hypofractionated radiotherapy regimens, with doses per fraction between 2.4-3.4 Gy. In addition, ultra-HypoAR regimens (fraction size ≥ 5 Gy) are also suggested as an alternative [5].

In the current study we report our clinical experience with image guided ultra-HypoAR delivered with Volumetric Modulated Arc Therapy (VMAT) technique for low-risk prostate cancer. A comparative radiobiological analysis of Dose-Volume histograms obtained for target volumes and organs at risk (OARs) performed, investigating the advantages and disadvantages of ultra-HypoAR and conventional radiotherapy regimens. Early clinical results on efficacy and toxicity are also reported.

Methods

We performed a radiobiological analysis of Dose-Volume Histograms (DVH) from the radiotherapy planning performed for the first 23 patients recruited in a prospective study of VMAT ultra-hypofractionated and accelerated radiotherapy (ultra-HypoAR) for low-risk prostate cancer. The study has been approved by the Institute Ethics and Research Committee (ES10 24-10-2018). All patients gave written informed consent.

All patients were treated at the Department of Radiotherapy and Oncology, University Hospital of Alexandroupolis, Democritus University of Thrace, Greece. For simulation and treatment, patients were immobilized in supine position by using a personalized knee-fix device and they have followed the same workflow taking the same instructions for an empty bowel and a confortable full bladder. The computed tomography (CT) set of images obtained by the CT-simulator was transferred to Monaco TPS version 5.1 (Elekta CMS, Maryland Heights, MO, USA), to outline the volumes of interests. The structures for analysis included the prostate, the seminal vesicles, the rectum and the bladder. The treatment plans were produced at the Monaco TPS version 5.1. Treatment was delivered by a 6 MV ELEKTA Infinity™ Linear Accelerator (Elekta, Stockholm, Sweden) endowed with an Agility™ head (Elekta, Stockholm, Sweden) and multileaf collimator (MLC) featuring 5mm leaves at the isocenter.

To avoid inter-physician and inter-physicist variability, the planning of all patients was performed by the head of the Department in collaboration with the radiotherapy physicists signing the current paper. Clinical target volume (CTV) was delineated for prostate and seminal vesicles and a non-uniform margin that was applied to the planning target volume (PTV) was created by expanding the CTV 0.7 mm laterally, 0.5 mm anteriorly and 0.3 mm posteriorly, respectively. Adjustments were subsequently performed by the responsible for the planning radiation oncologist. These adjustments refer to corrections of the software margin tool of Monaco. Each PTV was planned to receive at least 95% of the prescribed dose to 98% of its volume. For all patients two radiotherapy plans were conducted on the same contouring drawn for targets and organs at risk (OARs): i) the actual plan used for the treatment of patients with the ultra-HypoAR schedule and, ii) a plan of standard conventionally fractionated radiotherapy (CRT). The aim of the study was to compare the biological dose delivered to the target (PTV prostate and PTV seminal vesicles) and the relevant OARs, by the ultra-HypoAR vs. the CRT schedule. Patient and disease characteristics are shown in Table 1.

Radiotherapy technique

All patients were treated with a VMAT technique with IGRT. A cone-beam Computed Tomography (CBCT) was performed by ELEKTA Synergy kV CBCT (XVI) platform before each radiation treatment to check and adjust the position of patients. The alignment was made by the automatic registration algorithm Grey Value and if the in-charge doctor decided to adjust further the alignment then the manual method was used. Patients received

Table 1. Patient and Disease characteristics

Characteristics	*n*
Patients	23
Age, years (median/range)	76/58-80
T_{NM}-stage(*)	
$T_{1,2}$-N_0-M_0	23
Gleason score	
5-6	16
7	7
8-10	0
Androgen deprivation (**)	
No	13
Yes	10
Maximum PSA levels (***)	
Mean	8.2
Range	4.7-13.5
PSA levels before the onset of RT	
AD(***) no	
Mean	9.10
Range	4.8-13.5
AD yes (****)	
Mean	0.44
Range	0.01-1.4

(*) T-stage was assessed with prostate MRI, N-stage with abdominal CT and M-stage with bone-scintigraphy and CT-scans of the pelvis, abdomen and chest.
(**) patients had started androgen deprivation with LH-RH agonists with or without bicalutamide before the onset of radiotherapy. All patients interrupted hormonal therapy immediately before the onset of radiotherapy
(***) maximum values (ng/ml) before the onset of radiotherapy or hormonal therapy
(****) AD:Androgen deprivation before radiotherapy, no vs. yes

40.25 Gy, 5.75 Gy per fraction to the PTV prostate and 38,5 Gy, 5.5 Gy per fraction to the PTV seminal vesicles, for a total of 7 fractions, 2 fractions per week, within 22 days.

The cost functions that were used for each plan were the same. For PTVs we used two target penalties which are a physical cost functions and one quadratic overdose cost function which allows a max dose and an RMS (Root Mean Square) excess to be set. Target penalty is a quadratic penalty constraint which starts at the threshold dose. The first target penalty was set to prescribe 95% of total dose to 98% of minimum volume in order to have sufficient coverage. The second one was set to prescribe 100% of total dose to 50% of minimum volume in order to control the mean dose of the target. The quadratic overdose cost function was used for controlling the maximum dose of PTVs and was set to 100% of maximum dose with RMS 0.5 Gy. For OARs, bladder and rectum, was the serial cost function and the required parameters were 65% of total dose at Equivalent Uniform Dose, the power low exponent was set 12 and the shrink margin was set to 0.3 cm. Finally, the dose to the patient (body contour of patient) was controlled by using two quadratic overdose cost functions and a series of stepped shrink margins. The first one was set to 75% of maximum dose with RMS 0.5 Gy and shrink margin to 0.6 cm and the second one was set to 55% of maximum dose with RMS 0.5 Gy and shrink margin to 2.4 cm.

Radiobiological considerations – Normalized biological DVHs

The raw dosimetric data of prostate, bladder and rectum of the Dose- Volume Histogram (DVH) were extracted at an Excel worksheet. The volume scale was in percentage, the dose was in absolute scale and the bin width was set in 0.5 Gy.

To translate the physical-dose-based pDVH to biological-dose bDVH, the normalized total dose without and with time correction (NTD and NTD_T) formula [6,7], was applied for each point of the DVHs. This translates any fractionation and treatment acceleration to an equivalent (in terms of toxicity or efficacy) dose that would have been delivered with conventional fractionation (2 Gy/day). This equation is also known as Equivalent Dose in 2 Gy (EQD2).

The NTD_T formula is as follows:

$$NTD_{T\left(\frac{\alpha}{\beta}\right)} = D \cdot \frac{\frac{\alpha}{\beta} + d}{\frac{\alpha}{\beta} + 2Gy} + \lambda\,(T_c\text{-}T_o)$$

Where,
D: is the total dose of the altered fractionation scheme,
d: is the dose per fraction
α/β: is the ratio that provides the dose in Gray where cell killing from linear and quadratic components of the linear quadratic equation are equal.
λ: is the estimated daily dose consumed to compensate for rapid tumor repopulation
Tc: is the number of days required for the delivery of the NTD using conventional fractionation
To: is the number of days required for the delivery of the accelerated scheme.

The physical dose delivered to the PTV prostate and PTV seminal vesicles was 40.25 Gy and 38.50 Gy, respectively. To calculate the NTD for prostate cancer tissue we assumed an α/β-value of 2 Gy, as most studies suggest a mean value lower than 2 Gy [3,4]. This was 78 Gy and 72 Gy, respectively. An α/β-value of 4 Gy was considered for late normal rectum and bladder tissue toxicities, while an α/β-value of 10 Gy was considered for early rectum and bladder mucosa toxicities [8-10].

For a CRT scheme to deliver these doses to prostate cancer and seminal vesicles cancer, an overall-treatment time of 53 and 50 days, respectively, is demanded. Thus, the acceleration of radiotherapy applied by our HypoAR scheme (22 days) was 31 and 28 days, respectively. The λ-value for tumors and early responding tissues is postulated to be between 0.4-0.7 Gy/day and 0.2 Gy/day for late responding normal tissues [11]. As prostate cancer is, most often, a slowly growing tumor, we assumed a λ-value of 0.2 Gy/day, similar to the one of late responding tissues. Higher values would produce higher NTD_T to the tumor, further favoring ultra-HypoAR over CRT. Applying a λ-value of 0.2 Gy/day for tumor tissue, the NTD_T was 84 Gy and 78 Gy for prostate and seminal vesicles cancer tissue, respectively.

The above equations were applied to the prostate/seminal vesicles (anti-tumor efficacy), bladder and rectum (late and early responding tissue components) DVH data sets in order to find the equivalent doses in terms of conventional fractionation (NTD and NTD_T) for each point of the pDVH. In this way, we created a complete corrected set of bDVH data, that translate the ultra-HypoAR to a CRT scheme (with and without acceleration).

Conventional RT-planning

In order to compare our ultra-HypoAR NTDs and NTD_Ts bDVH values with a CRT scheme that would deliver the same NTD and NTD_T to the prostate cancer, we performed a conventional radiotherapy plan, using the same contouring of targets and organs. The CRT schedule included a two-phase regimen as follows: i) Initial arc comprising PTV prostate and PTV seminal vesicles for 72 Gy and 78 Gy for NTD and NTD_T respectively, 2 Gy/fraction and, ii. Booster arc confined to the PTV prostate for an extra 6 Gy, 2 Gy/fraction. The cost functions that we used were exactly the same with the ones of the delivered plan but customized for each prescription dose. Figure 1 present a typical DVH for one patient showing the coverage of PTV prostate and PTV seminal vesicles for hypofractionated and conventional plan. The raw data of bladder and rectum of pDVHs were extracted at an excel worksheet. As, even in CRT, each point of the pDVHs receive a distinct dose per fraction (lower than the maximum of 2 Gy), each point of the data set was introduced into the NTD and NTD_T equations to create the bDVHs of the CRT scheme.

Evaluation of radiotherapy toxicity and efficacy

Early toxicities were recorded twice-a-week (days of radiotherapy) during therapy and weekly thereafter for 2 months. Late toxicities were recorded every 6 months after completion of therapy. For acute bladder and rectum toxicity scoring we used the Radiation Therapy Oncolo-

gyGroup/European Organization for Research and Treatment of Cancer system [12]. For late toxicity we used subjective and objective scoring system proposed in the LENT-SOMA scale (Late Effects in Normal Tissues Subjective, Objective, Management and Analytic scale) [13].

The efficacy of radiotherapy was assessed by recording the PSA levels 2 months after radiotherapy and every 6 months thereafter.

Statistics

All data sets were imported to PRISM 8 (GraphPad Software Inc., 1994-2019 ©) for statistical analyses. We used the paired two-tailed t-test for the comparison between HypoAR and CRT schemes. Comparisons were performed for four dose-points of the bDVH, namely $D_{80\%}$, $D_{50\%}$, $D_{30\%}$ and $D_{10\%}$, where $D_{x\%}$ = dose delivered to the x% of the organ volume. Sigmoid dose/volume curves were

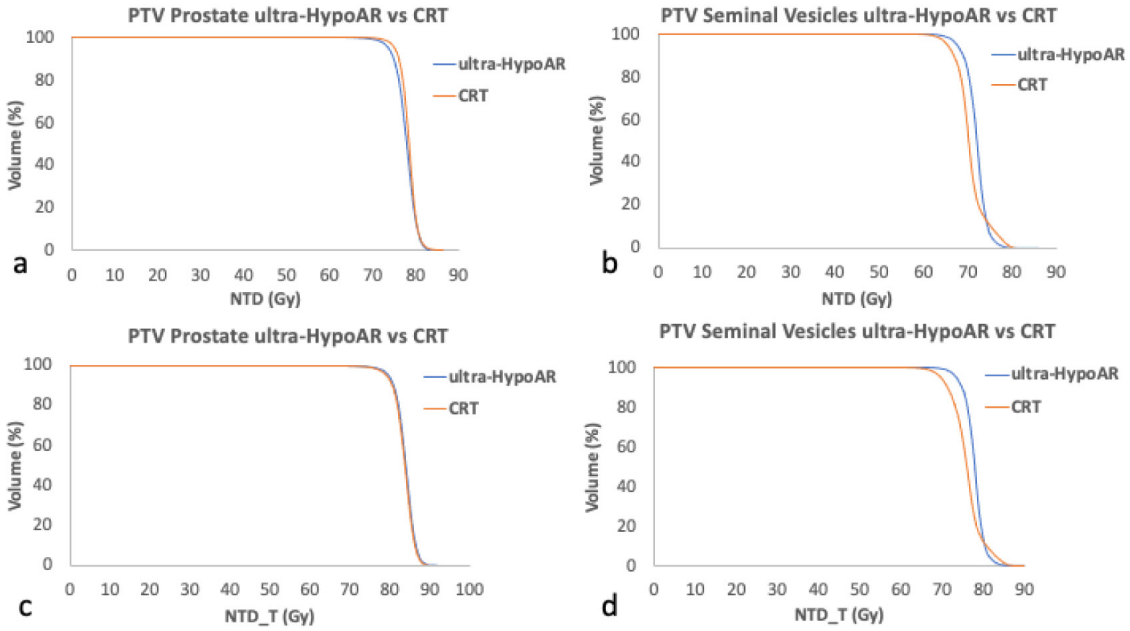

Figure 1. Comparison of PTV Prostate for HypoAR and CRT (α/β=2 Gy) without time correction **(a)** and with time correction **(c)** for one typical patient. Comparison of PTV Seminal vesicles for HypoAR and CRT (α/β=2 Gy) without time correction **(b)** and with time correction **(d)** for one typical patient.

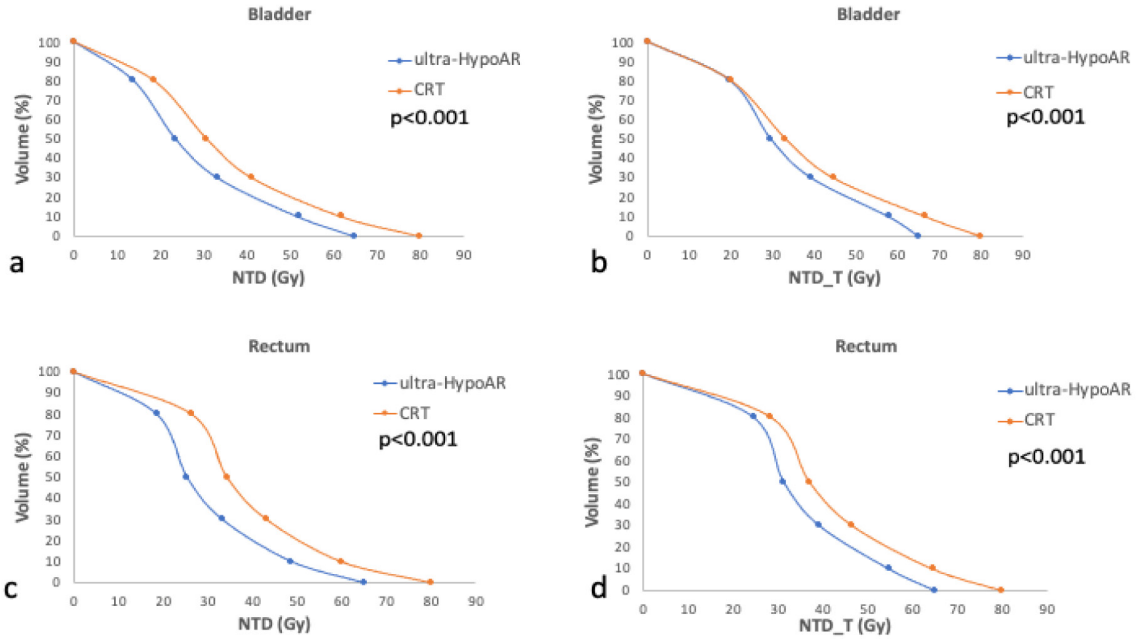

Figure 3. Comparison of 4 points ($D_{80\%}$, $D_{50\%}$, $D_{30\%}$, $D_{10\%}$) of average bladder DVH corrected for fractionation related to late toxicities (α/β=10 Gy) for HypoAR and CRT without time correction **(a)** and with time correction **(b)**. Comparison of 4 points ($D_{80\%}$, $D_{50\%}$, $D_{30\%}$, $D_{10\%}$) of average rectum DVH corrected for fractionation relate to late toxicities (α/β=10 Gy) for HypoAR and CRT without time correction **(c)** and with time correction **(d)**.

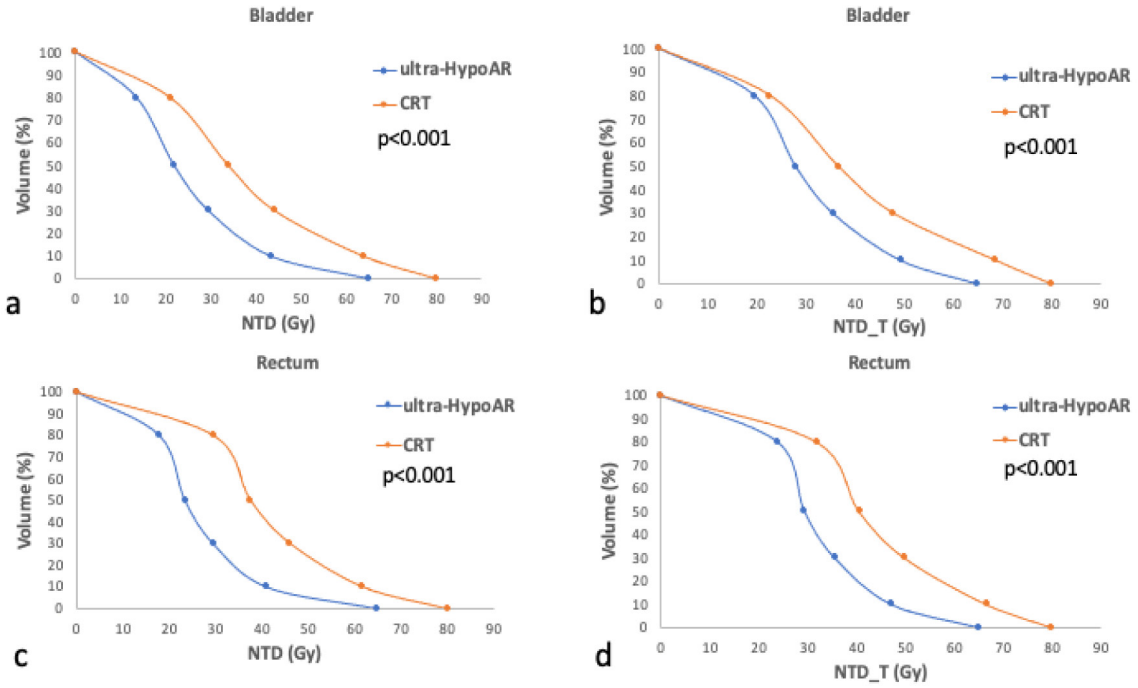

Figure 2. Comparison of 4 points ($D_{80\%}$, $D_{50\%}$, $D_{30\%}$, $D_{10\%}$) of average bladder DVH corrected for fractionation related to early toxicities (α/β=10 Gy) for HypoAR and CRT without time correction **(a)** and with time correction **(b)**. Comparison of 4 points ($D_{80\%}$, $D_{50\%}$, $D_{30\%}$, $D_{10\%}$) of average rectum DVH corrected for fractionation relate to early toxicities (α/β=10 Gy) for HypoAR and CRT without time correction **(c)** and with time correction **(d)**.

also drawn using a 3rd order polynomial equation and presented (GraphPad Prism logismic). A p value <0.05 was considered as statistically significant.

Results

By design, the CRT scheme provided the same NTD and NTD_T as the ultra-HypoAR one, assuming an α/β-ratio value for prostate cancer cells of 2 Gy. The question to answer was 0what would be the difference, in terms of late and early rectum and bladder toxicities, between the two schemes.

The NTD and NTD_T-based bDVH were calculated for bladder and rectum tissue late effects (α/β=4 Gy) and early effects (α/β=10 Gy). Ultra-HypoAR produced a significantly lower biological dose burden for the early responding tissue component of the bladder and rectum, whether calculated for time-correction or not, for both bladder and rectum (p<0.0001); Figure 2. bDVH curves predicted that late toxicities from bladder and rectum mucosa, are strikingly lower in the ultra-HypoAR regimen (p<0.0001); Figure 3. Tables 2 and 3 show comparative analysis of the NTD and NTD_T delivered to the late and early responding tissue components of bladder and rectum, for four organ volumes of the DVH (80%, 50%, 30% and 10%), by the ultra-HypoAR and CRT regimens. Again, all data favored the ultra-hypoAR regimen over the CRT one (p<0.001) except NTD_T80 of bladder for late toxicity effect (Table 3) which is meaningless because it refers to low doses.

In clinical practice, the ultra-HypoAR regimen showed an excellent tolerance in terms of early toxicity. All patients accomplished their treatment without delays. There was no case of early grade 3-4 toxicity recorded. Frequency grade 1 and 2 was noted in 14/23 and 0/23 patients, respectively and dysuria grade 1 and 2 in 15/23 and 0/23 patients, respectively. Proctitis grade 1 was recorded in 6/23 and grade 2 in 1/23 patients. Within a median of follow-up time of 14 months (12-24 months) there was no case with grade 2-4 late sequel. Two out of 23 cases reported grade 1 dysuria, and 2/23 grade 1 frequency. There was no patient reporting hematuria, incontinence or decreased stream.

None of the patients presented with biochemical relapse within the limited available follow-up interval. In patients who had not received androgen deprivation, the median PSA levels dropped from 9.1 to 0.75 and 0.45 ng/ml at 6 and 12 months, respectively, after the end of therapy.

Discussion

Radiotherapy is a standard therapeutic approach for the treatment of prostate cancer. The best fractionation, however, became a matter of biological and clinical debate during the past 20 years. This debate was triggered by radiobiological analysis of

Table 2. Comparison of average NTD and NTD_T received by early responding tissue components of the bladder and rectum (α/β=10), calculated at 80%, 50%, 30% and 10% of organ volumes (for α/β=10 Gy), between HypoAR and CRT delivering the same NTD and NTD_T to the prostate cancer (α/β=2 Gy)

					Bladder			
NTD (Gy)	*HypoAR80*	*CRT80*	*HypoAR50*	*CRT50*	*HypoAR30*	*CRT30*	*HypoAR10*	*CRT10*
Mean (Gy)	13,55	20,97	21,88	33,86	29,50	44,15	43,28	63,77
Std. Deviation	6,558	9,909	3,677	5,549	4,652	6,927	4,517	5,634
Range	20,92	29,57	14,92	22,68	18,45	26,59	16,37	21,46
p value	<0.0001	<0.0001	<0.0001	<0.0001				
					Bladder			
NTD_T (Gy)	*HypoAR80*	*CRT80*	*HypoAR50*	*CRT50*	*HypoAR30*	*CRT30*	*HypoAR10*	*CRT10*
Mean (Gy)	19,55	22,71	27,88	36,55	35,50	47,82	49,28	68,63
Std. Deviation	6,558	10,88	3,677	6,114	4,652	7,562	4,517	6,08
Range	20,92	34,39	14,92	24,73	18,45	27,76	16,37	23,15
p value	0,0036	<0.0001	<0.0001	<0.0001				
					Rectum			
NTD (Gy)	*HypoAR80*	*CRT80*	*HypoAR50*	*CRT50*	*HypoAR30*	*CRT30*	*HypoAR10*	*CRT10*
Mean (Gy)	17,89	29,45	23,40	37,48	29,53	46,10	41,07	61,77
Std. Deviation	1,859	2,603	1,891	2,678	3,111	4,161	3,667	4,626
Range	7,393	11,65	7,53	12,66	11,67	16,67	13,66	18,16
p value	<0.0001	<0.0001	<0.0001	<0.0001				
					Rectum			
NTD_T (Gy)	*HypoAR80*	*CRT80*	*HypoAR50*	*CRT50*	*HypoAR30*	*CRT30*	*HypoAR10*	*CRT10*
Mean (Gy)	23,89	31,82	29,40	40,58	35,53	49,86	47,07	66,56
Std. Deviation	1,859	3,085	1,891	3,383	3,111	4,862	3,667	4,989
Range	7,393	13,21	7,53	14,73	11,67	18,77	13,66	19,24
p value	<0.0001	<0.0001	<0.0001	<0.0001				

clinical data suggesting that the α/β-ratio of prostate cancer cells, is as low as 1 or 2 Gy [3,4]. This realization inevitably led to the hypothesis that large radiotherapy fractions may produce stronger anti-tumor effects, while at the same time toxicities from normal tissues that have a higher, about 4 Gy, α/β-ratio should remain low.

A large number of randomized trials gradually shifted the radiotherapy regimens towards accelerated and hypofractionated schemes. In 2018, a consensus from three leading medical societies became available [14-16], reporting the accepted guidelines for external beam radiotherapy schemes proposed for the treatment of localized early-stage prostate cancer. Overall, moderate hypofractionation, delivering daily fractions of up to 3.4 Gy, are considered equally effective and safe with CRT. A recent large population-based study from UK, confirmed that HypoAR does not increase the risk of gastrointestinal and urinary toxicities [17]. The reduction of the overall treatment time down to 3-5 weeks, instead of the 7-8 weeks of CRT, produces additional benefits as it lowers the discomfort of patients travelling to the Radiotherapy Departments, reduces the cost of radiotherapy and almost doubles the available LINAC positions eliminating waiting lists. Our long experience with 3.4 Gy/day fractionation confirms high efficacy and the excellent tolerance of ultra-HypoAR regimens [18,19].

Ultra-hypofractionation, with radiotherapy fractions higher than 5 Gy is widely applied, although the 2018 consensus recommendations suggest that such schedules are accepted for low-risk patients and should remain in the context of clinical trials for patients with an intermediate risk. IGRT techniques are strongly recommended [14-16]. In a recent randomized trial from Sweden and Denmark, Widmark et al compared an ultra-HypoAR scheme of 42.7 Gy delivered with 6.1 Gy/fraction (7 fractions, 3 fractions per week, in 2.5 weeks) with a CRT scheme of 78 Gy in 8 weeks [20]. The results support the use of ultra-HypoAR as the efficacy and late toxicity were similar in both groups, although early toxicity was higher in the accelerated scheme. In the Pace-B

Table 3. Comparison of average NTD and NTD_T received by late responding tissue components of the bladder and rectum (α/β=4), calculated at 80%, 50%, 30% and 10% of organ volumes (for α/β=4 Gy), between HypoAR and CRT schemes delivering the same NTD and NTD_T to the prostate cancer (α/β=2 Gy)

					Bladder			
NTD (Gy)	*HypoAR80*	*CRT80*	*HypoAR50*	*CRT50*	*HypoAR30*	*CRT30*	*HypoAR10*	*CRT10*
Mean (Gy)	13,80	18,52	23,51	30,72	33,23	41,13	51,88	61,91
Std. Deviation	7,203	9,095	4,507	5,519	6,122	7,291	6,166	6,168
Range	23,35	28,13	18,35	23,44	24,40	28,17	22,74	23,97
p value	<0.0001	<0.0001	<0.0001	<0.0001				
					Bladder			
NTD_T (Gy)	*HypoAR80*	*CRT80*	*HypoAR50*	*CRT50*	*HypoAR30*	*CRT30*	*HypoAR10*	*CRT10*
Mean (Gy)	19,80	20,03	29,51	33,15	39,23	44,56	57,88	66,82
Std. Deviation	7,203	9,94	4,507	6,04	6,122	7,883	6,166	6,627
Range	23,35	31,79	18,35	24,45	24,40	29,02	22,74	25,29
p value	0,7511	<0.0001	<0.0001	<0.0001				
					Rectum			
NTD (Gy)	*HypoAR80*	*CRT80*	*HypoAR50*	*CRT50*	*HypoAR30*	*CRT30*	*HypoAR10*	*CRT10*
Mean (Gy)	18,54	26,30	25,33	34,25	33,22	43,12	48,75	59,84
Std. Deviation	2,153	2,525	2,395	2,71	4,114	4,384	5,034	5,07
Range	7,988	11,31	9,56	12,82	15,33	17,33	18,82	19,81
p value	<0.0001	<0.0001	<0.0001	<0.0001				
					Rectum			
NTD_T (Gy)	*HypoAR80*	*CRT80*	*HypoAR50*	*CRT50*	*HypoAR30*	*CRT30*	*HypoAR10*	*CRT10*
Mean (Gy)	24,54	28,43	31,33	37,11	39,22	46,57	54,75	64,48
Std. Deviation	2,153	3,006	2,395	3,431	4,114	5,063	5,034	5,42
Range	7,988	12,91	9,56	14,96	15,33	19,54	18,82	20,97
p value	<0.0001	<0.0001	<0.0001	<0.0001				

UK trial, an ultra-HypoAR scheme delivering 25 Gy with 5 Gy fractions in 1-2 weeks was tested against 78 Gy of CRT [21]. Again, the authors found no increase in terms of acute toxicity. Two additional non-randomized trial from Spain and Italy reported good tolerance and high efficacy [22,23].

In the current interim report of a prospective trial, radiobiological analysis of an ultra-HypoAR regimen delivering 7 fractions of 5.75 Gy in 3.5 weeks, show that the predicted early and late toxicity of bladder and rectum with ultra-HypoAR is lower than a CRT scheme that would deliver the same biological dose to the PTV, whether time corrected or not. Radiobiological calculations were performed assuming an α/β ratio for cancer of 2 Gy, and for the normal tissue early and late effects of 10 Gy and 4 Gy, respectively. The λ-value of prostate cancer is unknown. The 0.2 Gy/day λ-value for cancer tissues, considered in the current analysis, is rather at the lower limits, as tumors λ-value is expected to be higher [24]. If higher cancer λ-values are to be applied in the current analysis, the difference in terms of late and early bladder and rectum toxicities would further broaden in favor of ultra-HypoAR.

Our clinical experience with the herein analyzed ultra-HypoAR regimen is encouraging and along with other published trials. Early toxicity was minimal and our findings do not agree with the increased early toxicity found in the study by Widmark et al. The total dose, however, given in our study is lower (40.25 Gy vs. 42.7 Gy) and the overall treatment time is longer (3.5 weeks vs. 2.5 weeks). This may explain the very low early toxicity recorded in our analysis. We have recorded no severe late toxicities, although the follow-up is too short for safe conclusions.

In conclusion, radiobiological analysis of DVHs and preliminary clinical experience predict for a better efficacy and low early and late toxicity profile for the tested seven fraction-IGRT-VMAT ultra-HypoAR regimen.

Conflict of interests

The authors declare no conflict of interests.

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