Early toxicity of hypofractionated radiotherapy for prostate cancer

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Background. Hypofractionated accelerated radiotherapy (HART) is now a feasible option for prostate cancer treatment apropos toxicity, biochemical control and shortening of treatment. The aim of this study was to investigate hypofractionated schedules in the treatment of patients with localized prostate cancer.

Patients and Methods. Between 2011-2014, 158 patients were treated using the RapidArc technique with IGRT. The target volume for low risk patients was the prostate alone with a prescribed dose of 20x3.0 Gy (EQD2=77 Gy). Targets volumes for intermediate and high risk patients were prostate and two thirds of the seminal vesicles with a prescribed dose 21-22x3.0/2.1 Gy (EQD2=81/45.4-84.9/47.5). Based on radiobiological modelling of early toxicity, we used four fractions per week in the low risk group and four fractions in odd weeks and three fractions in even weeks in intermediate and high risk groups. The RTOG/EORTC toxicity scale was used.

Results. Early genitourinary (GU) toxicity was observed for grades 0, 1, 2, 3 and 4 in 73 (46%), 60 (38%), 22 (14%), 0 and 3 (2%), respectively; early gastrointestinal (GI) toxicity was recorded for grades 0, 1, 2 and 3 in 119 (75%), 37 (23%), and 2 (1%) patients, respectively.

Conclusion. A combination of moderate hypofractionation, number of fractions per week adapted to target volume and precise dose delivery technique with image guidance appears safe with low early toxicity. Longer follow up is needed to assess late toxicity and tumor control probability.

Key words: hypofractionation, VMAT, volumetric arc therapy, RapidArc, Tumor control probability, Normal tissue complication probability, alternated time schedule

Received: September 13, 2015; Accepted with revision: February 10, 2016; Available online: March 4, 2016
<http://dx.doi.org/10.5507/bp.2016.008>

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INTRODUCTION

Prostate cancer is now one of the most common malignant diseases in men in the USA. Expansion of PSA screening has led to a remarkable rise in low-risk prostate cancer detection¹. Conventional fractionated radiotherapy, provided for eight weeks, is one of the longest schedules in radiation oncology practice. Shortening the overall treatment period is advantageous from many points of view, including patient compliance and economic considerations. Increasing numbers of clinical trials discussed below show the non-inferiority of hypofractionated accelerated radiotherapy (HART) in comparison to conventionally fractionated curative radiotherapy of prostate cancer. From the radiobiology point of view, the most important is the α/β ratio, which appears to be much lower for prostate cancer than for other tumors. Moreover, it appears to be even lower than the value of late reacting tissues². The most frequently published value is $\alpha/\beta=1.5$ Gy (ref.³). The lower the α/β ratio is, the higher the response to increased dose per fraction of ionizing radiation. In other words, the same equivalent dose to tumor and lower equivalent dose to surrounding tissues, including these responsible for late toxicity, may be achieved by HART. This assumption is supported by a number of current clinical

studies^{4,7}. However, with increasing dose per fraction, the probability of early toxicity rises. Extracranial Stereotactic radiotherapy uses high doses per fraction, usually 7–10 Gy in 4–5 fractions. Precise dose delivery and image guidance systems, mostly using robotic linear accelerator and automatic fiducials tracking, are used. Mild hypofractionation uses lower doses per fraction, usually 2.5–4 Gy. Taking into account the phenomenon of repopulation, we assume that partial reduction of early effects may be achieved by inserting free days into the fractionation schedule². The aim of this study was to confirm that the hypofractionated regimens used were feasible without undue early toxicity and with perspective to show acceptable late toxicities and disease control.

PATIENTS AND METHODS

Patients

Between January 2011 and March 2014, 158 patients with localized, histologically confirmed prostate adenocarcinoma were treated at the Masaryk Memorial Cancer Institute in Brno, Czech Republic with volumetric modulated arc therapy (RapidArc) (ref.⁸). Patients were stratified into two risk groups according to NCCN clinical

guidelines in oncology, Prostate cancer, version 1.2011 (ref.⁹) as low risk (PSA < 10 ng/mL, GS ≤ 6, T1-T2a) as one group and intermediate risk (PSA 10 -20 ng/mL or GS = 7 or T2b-T2c) and high risk (PSA > 20 ng/mL, or GS > 7, or T3a) together as the second group. This classification was based on the work of D'Amico et al.¹⁰. Basic patient characteristics are summarized in Table 1.

Schedule preparation

In preparing the HART schedule, dose volume histograms of 80 patients were analyzed using the methods of radiobiological modeling of normal tissue complication probability (NTCP) and tumor control probability (TCP) (ref.¹¹). We searched for a universal scheme that met the criteria for isoeffectiveness (TCP) and isototoxicity (NTCP) evaluated for early and late toxicity for rectum and bladder. For late toxicity, Quantec^{12,13} data were used. For early toxicity we used data published by Strigari et al. Radiobiological modeling was performed with the Biogray software¹⁴. For each DVH a set of TCP and NTCP values was obtained. Then we searched for an appropriate schedule with 3.0 Gy per dose. The models used took into account the repopulation factor. In this way, early toxicity depending on number of free days per week could be modeled. Two separate schedules for different irradiated volumes (for prostate alone and for prostate and two thirds

of the seminal vesicles) were created. For prostate alone, the final scheme was 20x3.0 Gy, 4 days per week (77 Gy with conventional fractionation). For irradiating the prostate and 2/3 of the seminal vesicles as PTV1 and prostate alone as PTV2, the prescribed doses were 21-22 x 3.0 Gy for PTV2 a and 21-22 x 2.1 Gy for PTV1, alternately 3 and 4 days per week, using simultaneous integrated boost technique. The doses corresponded to 81-84.9 Gy and 45.4-47.5 Gy with conventional fractionation.

Radiotherapy planning and patient preparation

Standard planning CT study of pelvis with 3 mm slice thickness was performed with iodine contrast agent administered half an hour before scanning. After administration, patients were instructed to urinate and drink 0.5 L of water, in order to have a comfortably full bladder at the time of CT scanning. Organs at risk (bladder, rectum from anal sphincter to sigmoid junction and both femoral heads) were contoured by a radiation oncologist. In low risk patients, clinical target volume included prostate alone, while in intermediate and high risk patients, two clinical target volumes were defined - prostate with two thirds of the seminal vesicles and prostate alone. Image of contrast agent in bladder was used to precisely differentiate the border between bladder and prostate prominence, if present. In order to calculate the correct dose margin,

Table 1. Patient's characteristics.

	Low risk	Intermediate and high risk	All
Number of patients	48	110	158
Median of age	74	75	74
Median of follow-up (months)	28	20	22
Median of PSA (ng/mL)	6.4	9.1	7.6
Gleason score (GS)			
GS = 3	1 (2%)	1 (1%)	2 (1%)
GS = 4	1 (2%)	0 (0%)	1 (1%)
GS = 5	6 (13%)	1 (1%)	7 (4%)
GS = 6	40 (83%)	29 (26%)	69 (44%)
GS = 7	0 (0%)	72 (65%)	72 (46%)
GS = 8	0 (0%)	5 (5%)	5 (3%)
GS = 9	0 (0%)	2 (2%)	2 (1%)
T Stage			
T1	39 (81%)	61 (56%)	100 (63%)
T2	9 (19%)	45 (41%)	54 (34%)
T3	0 (0%)	4 (3%)	4 (3%)
N1 Stage	0 (0%)	0 (0%)	0 (0%)
Hormonal therapy	20 (42%)	65 (59%)	85 (54%)
Intervention on prostate (transurethral or retropubic)	2 (4%)	2 (2%)	4 (3%)
Risk Group (NCCN)			
Low risk	48 (100%)	0 (0%)	48 (30%)
Intermediate risk	0 (0%)	94 (85%)	94 (59%)
High risk	0 (0%)	16 (15%)	16 (10%)
Applied dose			
20x3.0 Gy	48 (100%)	0 (0%)	48 (30%)
21x3.0 Gy	0 (0%)	71 (65%)	71 (45%)
22x3.0 Gy	0 (0%)	39 (35%)	39 (25%)

the volume of contrast agent in CT image was substituted with water-density equivalent. CTV-PTV was 10 mm in all directions except for 8 mm towards the rectum in compliance with internal IGRT protocol. Prescribed doses are summarized above.

Dose-volume constraints for organs at risk are summarized in Table 2. For all patients, volumetric modulated RapidArc technique was planned with Aria 8.6 (2011-2013) and Aria 8.11 (2014). The dose was delivered by Clinac iX (Varian).

To prevent early toxicity, treatment for low-risk cancer was performed four days per week (with Wednesday typically as the free day), and for intermediate/high-risk alternately three and four days per week (usually Wednesday in odd weeks and Tuesday and Thursday in even weeks as free days). During therapy, daily cone beam CT was performed for image guidance purposes. Cone beam CT and planning CT images were co-registered based on soft tissue. Position correction was made every day with no action threshold using self-acting Table movement. Before each fraction, patients were asked to defecate, if possible, and exactly half an hour before irradiation to urinate and then drink 0.5 L of water. Patients underwent a regular weekly clinical examination for assessment of early toxicity. The worst grade observed during radiotherapy was recorded as a definitive early toxicity grade. The follow up visits were performed on the 1st, 3rd and then every 6th month after radiotherapy was terminated, or more frequently, according to physician decision. Toxicity was evaluated according to the RTOG/ EORTC scale¹⁵. Patients who needed any kind of drug support were classified as G2. Three patients who needed urethral catheterization, were identified as G4.

Statistical analysis

In this study, descriptive statistics (average, median, frequency) were used.

RESULTS

Low-risk patients

48 patients with low-risk cancer underwent therapy on the prostate alone. 20 (42%) of these were treated with neoadjuvant hormonal therapy administered by a urologist. Two (4%) patients had transurethral prostatectomy in their medical history. Early genitourinary (GU) toxicity

Table 2. Dose-volume constraints.

	Maximal dose [Gy] (in volume of organ)
Rectum	63 (15%)
	58 (20%)
	54 (25%)
	50 (35%)
	42 (50%)
Bladder	68 (15%)
	63 (25%)
	59 (35%)
	55 (50%)
Femoral heads	42 (5%)

was observed for grades 0, 1, 2, 3 and 4 in 20 (42%), 18 (38%), 9 (19%), 0 and 1 (1%), respectively; early gastrointestinal (GI) toxicity was recorded for grades 0, 1 and 2 in 31 (65%), 16 (33%) and 1 (2%) patients respectively.

Intermediate and high-risk patients

94 patients with intermediate and 16 with high-risk cancer underwent therapy on prostate alone as one and prostate and 2/3 of seminal vesicles as the second target volume. 65 (59%) of these were treated with neoadjuvant and concomitant hormonal therapy. Two (2%) patients had transurethral prostatectomy in their medical history. Early genitourinary (GU) toxicity was observed for grades 0, 1, 2, 3 and 4 in 53 (48%), 42 (38%), 13 (12%), 0 and 2 (2%), respectively; Early gastrointestinal (GI) toxicity was recorded for grades 0, 1, and 2 in 88 (80%), 21 (19%), 1 (1%) and 0 patients, respectively.

Cumulative results of all patients

Altogether, 158 patients with localized prostate cancer were treated with hypofractionated schedule. 85 (54%) were administered with neoadjuvant and 65 (41%) with concomitant hormonal treatment as well. Early genitourinary (GU) toxicity was observed for grades 0, 1, 2, 3 and 4 in 73 (46%), 60 (38%), 22 (14%), 0 and 3 (2%), respectively; early gastrointestinal (GI) toxicity was recorded for grades 0, 1, 2 and 3 in 119 (75%), 37 (23%), and 2 (1%) patients, respectively.

The results are summarized in Table 3.

Table 3. Early toxicity.

	Low risk		Intermediate + high risk		All	
	GI	GU	GI	GU	GI	GU
G0	31 (65%)	20 (42%)	88 (80%)	53 (48%)	119 (75%)	73 (46%)
G1	16 (33%)	18 (38%)	21 (19%)	42 (38%)	37 (23%)	60 (38%)
G2	1 (2%)	9 (19%)	1 (1%)	13 (12%)	2 (1%)	22 (14%)
G3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
G4	0 (0%)	1 (1%)	0 (0%)	2 (2%)	0 (0%)	3 (2%)

Table 4. Study comparison.

Reference	Year	n	N	d [Gy]	D [Gy]	EQD2 (a/b=1.5 Gy)	Technique	IGRT	CTV-PTV margins	Acute toxicity ≥G2 [%]		Acute toxicity ≥G3 [%]	
										GI	GU	GI	GU
Kitamura et al. ²⁴	2003	31	28	2.8	70	96.3	IMRT	+	3 mm, 1 mm posterior	0	5.8	0	0
Lukka et al. ⁴	2005	466	20	2.62	52.5	61.7	2D	-	10-15 mm	19.3	NA	4.3	9.2
Soete et al. ²⁵	2006	36	16	3.5	56	80	3D CRT, IMRT		3-10 mm	36	44	0	0
Junius et al. ²⁶	2007	38	25	2.64	66	78.1	IMRT	+	5-10 mm	16	26	0	0
Martin et al. ²⁷	2007	92	20	3	60	77.1	IMRT	+	7-10 mm	12	25	1	0
Leborgne and Fowler ²⁸	2008	56	20	3	60	77.1	3D CRT	-	5-11 mm	4.5	23	NA	NA
		20	20	3.15	60	83.7		-		29	29		
Arcangeli et al. ²⁹	2010	168	20	3.1	62	81.5	3D CRT	-	6-10 mm	35	40	0	3.33
Jerezek-Fossa et al. ²²	2011	179	26	2.7	70.2	84.2	3D Arc	+	3-7 mm	12.3	44.1	1.1	5
Lock et al. ³⁰	2011	66	20	3.16	63.2	84.1	IMRT	+	3-7 mm	35	43	10	9
Pollack et al. ²⁰	2013	151	26	2.7	70.2	84.2	IMRT	-	3 and 7 mm	18	48	0	8
Viani et al. ³¹	2013	112	23	3	69	88.7	3D CRT	-	7 and 10 mm	20.5	24.2	1.8	4.5
Aluwini et al. ²³	2015	410	19	3.4	64.6	90.4	IMRT	+-	3-10 mm	42	61	6	20
Madsen et al. ³²	2007	40	5	6.7	33.5	78.5	3D	+	4-5 mm	13	23	0	2.5
McBride et al. ³³	2012	45	5	7.25	36.25	90.6	CyberKnife	+	5 mm, 3 mm posterior	7	19	0	0
Boike et al. ³⁴	2011	15	5	9	45	135		+		0	27	0	0
		15	5	9.5	47.5	149.3	Tomotherapy	+	3 mm	27	7	0	0
		15	5	10	50	164.3		+		7	33	0	0
Loblaw et al. ³⁵	2013	84	5	7	35	85	IMRT	+	4 mm	10	20	0	1
Alongi et al. ³⁶	2013	40	5	7	35	85	VMAT	+	3-5 mm	10	40	0	0
Chen et al. ³⁷	2013	100	5	7 or 7.3	35 or 36.5	85 or 91.8	CyberKnife	+	5 mm, 3 mm posterior	1	25	0	0
Kang et al. ³⁸	2011	44	4	8 or 8.5 or 9	32 or 34 or 36	86.9 or 97.1 or 108	CyberKnife	+	4 mm, 2 mm posterior	9	14	0	0
Lee et al. ³⁹	2012	29	5	7.2	36	89.5	CyberKnife	+	5 mm, 2-3 mm posterior	3	24	0	0
Oliai et al. ⁴⁰	2013	70	5	7 or 7.25 or 7.5	35 or 36.25 or 37.5	85 or 90.6 or 96.4	CyberKnife	+	5 mm, 3 mm posterior	4	23	0	4
Katz et al. ⁴¹	2013	304	5	7 or 7.25	35 or 36.25	85 or 90.6	CyberKnife	+	5 mm, 3 mm posterior	4	5	0	0
Bolzicco et al. ⁴²	2013	100	5	7	35	85	CyberKnife	+	5 mm, 3 mm posterior	18	12	0	0

n=number of patient in hypofractionated arm; N=number of fraction; d=particular dose; D=total dose; EQD2=dose equivalent to 2Gy fractionation; NA=not available

DISCUSSION

Technological progress in accuracy of radiation delivery dose enables reduction in irradiated volumes. This improvement enables application of different accelerated regimens and schedules, from mild hypofractionation to stereotactic techniques. Higher precision of dose delivery and image guidance is one approach for accelerated fractionation schedules. In prostate cancer, we there is another assumption which is supported by different radiobiological characteristics. The concept that prostate cancer's α/β ratio is lower than α/β of rectum and bladder, was published by Brenner and Hall¹⁶. A number of other studies suggested high sensitivity dose per fraction. These would favor hypofractionated schedules¹⁷⁻¹⁹. Dasu and Toma-Dasu³ analyzed the clinical data of 14 168 patients and concluded, that the α/β ratio is very low (1-1.7 Gy). In tumors with high α/β value, the late toxicity NTCP increases with increasing dose per fraction, while the TCP increases much more slowly. Reverse ratio is applicable in prostate cancer radiotherapy. With increasing prescribed daily dose, the TCP curve should increase faster than NTCP. Taking into account healthy tissues repopulation, we assume that early toxicity can be reduced by using less than five fractions per week. Owing to larger irradiated volume (seminal vesicles) and higher total dose in intermediate and high-risk patients, one and two free days a week alternately were needed to reach the isotoxic scheme in our radiobiological modeling, while only one free day was needed when prostate alone was irradiated.

The concept of hypofractionation has been tested in a few randomized and nonrandomized trials. The authors concerned have described early as well as chronic toxicity, as low or acceptable.

Arcangeli et al.⁶ tested a regimen with 20x3.1 Gy, 4 fractions per week versus 40x2.0 Gy in patients with high-risk prostate cancer. Whole pelvis was not irradiated. No significant difference in toxicity was observed. With a median follow-up of 70 months, isoefficiency of both fractionation schedules was confirmed.

Pollack et al.²⁰ actualized the data of their randomized study which compared regimens 38x2.0 Gy versus 26x2.7 Gy. No significant difference was found in toxicity or in biochemical control.

Faria et al.²¹ assessed 82 patients with intermediate risk prostate cancer without any hormonal therapy with a median follow up of 81 months. The applied dose was 22x3.0 Gy, 3D CRT technique, 7 mm CTV-PTV margin. G2 toxicity for GI was 18% and for GU 21% (worst recorded grade). In the last clinical evaluation, the level of G2 toxicity decreased to 2% and 7%, respectively.

Jereczek-Fossa et al.²² assessed a group of 179 older men (median age 74 years) treated with dose 26x2.7 Gy with IGRT and smaller CTV-PTV margin versus 174 younger (median age 71 years) treated with a dose of 42x2.0 Gy without IGRT and bigger CTV-PTV margin. GI toxicity grade 2 or higher was recorded in 12.3% patients treated with hypofractionation and 6.3% patients treated with conventional fractionation ($P = 0.014$), GU toxicity was 39.2% and 20.7% respectively ($P < 0.0001$).

Fig. 1. Early toxicity distribution.

Fig. 2. Incidence of early toxicity $\geq$ G2.

Aluwini et al.²³ recently published results of phase III randomized study, enrolling patients with intermediate or high risk prostate cancer. 391 patients received 39x2.0 Gy, five fractions per week and 403 patients received 19x3.4 Gy, three fractions per week. IMRT with IGRT focusing on applied fiducial markers was used. Early GU toxicity worse than G2 was 58% versus 61% ($P = 0.43$) and GI toxicity 31% versus 42% ($P = 0.0015$) for conventional fractionation versus hypofractionation respectively.

Trials using extreme hypofractionated schedules show overall low early toxicity. Most of them use robotic linear accelerator, image guidance with fiducials tracking and very small CTV-PTV margins or special immobilisation techniques.

These and other studies are summarized in Table 4.

These studies are difficult to compare owing to different dose delivery techniques, dose per fraction, usage of IGRT, etc. It can be said that most studies show mild early GI (4.5-42%) and GU (7.6-61%) toxicity $\geq$ G2.

In comparison to the studies mentioned above, our study achieved low levels of early toxicity. This can be explained by choice of free days inserted into the schedule in combination with precise dose delivery represented by volumetric arc technique with daily cone beam image guidance.

Smaller CTV-PTV margins used contemporary in our clinic can show further lowering of early toxicity.

From a radiotherapy clinic time management point of view, the concept of free days can be better optimized.

One example is a schedule with alternating two and three radiation days per week and dose per fraction which will preserve corresponding equivalent dose, as well as shorten all treatment periods in comparison with conventional fractionation.

CONCLUSION

This study confirms the feasibility of hypofractionated approach in the management of prostate cancer curative radiotherapy from the viewpoint of early toxicity. The dose 20-22x3.0 Gy, three to four days per week, is associated with acceptable early toxicity. Late toxicity and PSA response is not reported due to short follow-up.

Use of radiobiological principles in combination with precise dose delivery and image guidance systems is promising in terms of to very short radiotherapy course to the advantage of patients, hospitals and the public health system.

ABBREVIATIONS

3D-CRT, 3D Conformal Radiotherapy; d, Dose per fraction; D, Total dose; DVH, Dose volume histogram; EQD2, Dose equivalent to 2Gy fractionation; GI, Gastrointestinal; GS, Gleason Score; GU, Genitourinary; HART, Hypofractionated Accelerated Radiotherapy; IGRT, Image Guided Radiotherapy; IMRT, Intensity Modulated Radiotherapy; NCCN, National Comprehensive Cancer Network.

Acknowledgement: This article is dedicated to the grant LO 1413.

Author contributions: All authors contributed equally to preparing the manuscript.

Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

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