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Clinical Investigation

Moderate Hypofractionated Protracted Radiation Therapy and Dose Escalation for Prostate Cancer: Do Dose and Overall Treatment Time Matter?

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Summary

This report compares, retrospectively, the 5-year treatment outcomes and toxicity rates of 2 sequential dose escalation regimens of twice-weekly 4 Gy/fractions hypofractionated intensity modulated radiation therapy in patients with localized prostate cancer. A single 4-Gy additional fraction in patients treated with 14 × 4 Gy resulted in a similar and minimal acute toxicity, in worse moderate to severe urinary and gastrointestinal late effects, but a significantly better biochemical control.

Purpose: This was a retrospective study of 2 sequential dose escalation regimens of twice-weekly 4 Gy/fractions hypofractionated intensity modulated radiation therapy (IMRT): 56 Gy and 60 Gy delivered within a protracted overall treatment time (OTT) of 6.5 and 7 weeks, respectively.

Methods and Materials: 163 prostate cancer patients with cT1c-T3a disease and nodal involvement risk ≤20% (Roach index) were treated twice weekly to the prostate ± seminal vesicles with 2 sequential dose-escalated IMRT schedules: 56 Gy (14 × 4 Gy, n = 81) from 2003 to 2007 and 60 Gy (15 × 4 Gy, n = 82) from 2006 to 2010. Patient repositioning was made with bone matching on portal images. Gastrointestinal (GI) and genitourinary (GU) toxicities were scored according to the Common Terminology Criteria for Adverse Events version 3.0 grading scale.

Results: There were no significant differences regarding the acute GU and GI toxicities in the 2 dose groups. The median follow-up times were 80.2 months (range, 4.5-121 months) and 56.5 months (range, 1.4-91.2 months) for patients treated to 56 and 60 Gy, respectively. The 5-year grade ≥2 late GU toxicity-free survivals with 56 Gy and 60 Gy were 96 ± 2.3% and 78.2 ± 5.1% ($P = .001$), respectively. The 5-year grade ≥2 late GI toxicity-free survivals with 56 Gy and 60 Gy were 98.6 ± 1.3% and 85.1 ± 4.5% ($P = .005$), respectively. Patients treated with 56 Gy showed a 5-year biochemical progression-free survival (bPFS) of 80.8 ± 4.7%, worse than patients treated with 60 Gy (93.2 ± 3.9%, $P = .007$). A trend for a better 5-year distant metastasis-free survival was observed among patients treated in the high-dose group (95.3 ± 2.7% vs 100%, $P = .073$, respectively). On multivariate analysis, only the 60-Gy group predicted for a better bPFS ($P = .016$, hazard ratio = 4.58).

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Conclusions: A single 4-Gy additional fraction in patients treated with a hypofractionated protracted IMRT schedule of 14 × 4 Gy resulted in a similar and minimal acute toxicity, in worse moderate to severe urinary and GI late effects, but a significantly better biochemical control.

Introduction

Phase 3 randomized trials have shown that in localized or locally advanced prostate cancer dose escalation, with normofractionation (ie, 1.8-2 Gy per fraction), can result in improved 5-year biochemical control rates (1-3), which continue to be significant even after 8 to 10 years of follow-up (4-7). External beam radiation therapy (EBRT) dose escalation using a 3-dimensional conformal technique is limited by the increased rates of bowel and urinary toxicities (2, 8-12). To minimize such toxicities, biological dose escalation can be reached with the use of moderate hypofractionation (>2 Gy/fraction) in combination with contemporary planning and treatment delivery optimization techniques.

Dose escalation with hypofractionation is achievable because the α/β ratio of prostate cancer is estimated to be below 2 Gy (13, 14), with several studies concluding that normofractionated and hypofractionated regimens have comparable late toxicity profiles (15-17). However, there is only scarce evidence that compares between hypofractionated schedules evaluating toxicity and clinical outcomes (18). An ideal dose-fractionation-time for an optimal therapeutic ratio with >2 Gy/fraction for prostate cancer is presently unknown. Indeed, most hypofractionated schedules reported so far have been delivered in 4 to 5.5 weeks, a much shorter overall treatment time (OTT) than the usual 8 to 9.5 weeks used for standard fractionated regimens. Analyses of data on dose escalation using 3-dimensional conformal radiation therapy have suggested a benefit of 2.2% in biochemical control for every 1-Gy increase in dose level (9, 19), the dose-response relationship being linear between 64 Gy and 80 Gy. The plateau of this curve, where 100% local control is achieved, is hypothesized to be reached between 86.5 Gy and 95.5 Gy (9).

This report describes 2 sequential dose escalation regimens of twice-weekly hypofractionated schedules: 56 Gy in 14 × 4 Gy and 60 Gy in 15 × 4 Gy delivered within a protracted OTT of 6.5 and 7 weeks, respectively.

Methods and Materials

This was a retrospective study of 163 patients treated at the Geneva University Hospital (GVA) and at the Teknon Oncologic Institute in Barcelona (BCN), both sharing the same medical management (RM) and treatment strategy for prostate cancer. Patients with diagnoses of clinical stage cT1 to cT3a, cN0, cM0 (2010 American Joint Committee on Cancer staging system) localized prostate cancer were recruited. Patients shared a lymph node risk of <20% (according to Roach et al. [20]) and no cT3b disease, thus with no indication for elective pelvic lymph node irradiation. Patients with a Gleason score of 7, a prostate-specific antigen (PSA) level ≥10 ng/mL, or both were further investigated with an abdominal computed tomographic (CT) scan and a bone scan, to ensure there was no subclinical distant disease, and 141 patients (86.5%) benefited from contrast-enhanced endorectal magnetic resonance imaging. There were no differences between the 2 dose groups regarding the patients' prognostic characteristics as summarized in Table 1.

The clinical target volume (CTV) included the prostate gland with the seminal vesicles if their calculated risk of disease was >15% (according to Roach: [SV + (%) = (Gleason score-6) × 10 + PSA]). The planning target volume (PTV) was created from applying to the CTV a 10-mm margin in all directions, except posteriorly, where a reduced margin of 6 mm was used. The organs at risk (OAR) contoured were the rectum, the bladder, the penile bulb, and the femoral heads including the trochanter.

Table 1 Patient and tumor characteristics (n=63)

Characteristic	56 Gy	60 Gy	*P* value
Patients	81	82	
Age, y			
Median (range)	67.7 (51-86)	69.5 (53-82)	.439
PSA at diagnosis (ng/mL) (n=161)			
<10	66 (81.5)	63 (78.8)	.906
10-20	14 (17.3)	16 (20)	
≥20	1 (1.2%)	1 (1.2%)	
Median (range)	8.0 (1.6-30)	6.7 (1.4-27.3)	
AJCC cT stage			
Tx	1 (1.2)	2 (2.4)	.944
T1	40 (49.4)	39 (47.9)	
T2	28 (34.6)	28 (34.1)	
T3a	12 (14.8)	13 (15.9)	
Gleason score			
≤6	53 (65.4)	48 (58.5)	.421
7	28 (34.6)	34 (41.5)	
NCCN risk group (erMRI based for T3)			
Low	24 (29.6)	23 (28.0)	.975
Intermediate	32 (39.5)	33 (40.2)	
High	25 (30.9)	26 (31.7)	
ADT			
Yes	12 (14.8)	31 (37.8)	.001
No	69 (85.2)	51 (62.2)	

Abbreviations: ADT = androgen deprivation therapy; AJCC = American Joint Committee on Cancer; erMRI = endorectal magnetic resonance imaging; PSA = prostate-specific antigen.

Patients were treated twice weekly with 2 sequential dose-escalated IMRT schedules: 56 Gy (14 × 4 Gy, OTT 6.5 weeks) from 2003 to 2007 (21) and 60 Gy (15 × 4 Gy, OTT 7 weeks) from 2006 to 2010. The corresponding NTD_{2Gy} with an α/β ratio of 1.5 Gy, is 88 for the 56-Gy group and 94 for the 60-Gy group. The dose was prescribed to the PTV according to the International Commission on Radiation Units and Measurement reference point. The upper limit of the acceptable dose received by the PTV (D_{max}) was 110% of the prescribed dose, and the lower limit—that is, the minimum dose received (D_{min})—was 95% of the prescribed dose, which was allowed to be compromised to respect the OAR dose-volume constraints. The most important dose constraints used for dose optimization to the rectum and bladder were the following: V90% $\leq$ 30% and V50% $\leq$ 50% (Vx% = percentage of volume receiving x% of the dose). The above-described treatment planning conditions were valid for both treatment centers.

Regarding the treatment technique used, overall 134 (82.2%) patients were treated with IMRT (6 MV photon beams), 38 in GVA and 96 in BCN. In addition, in BCN 7 patients were treated with dynamic arc therapy (DAT) and the rest with a combination of DAT and IMRT. The number of beams ranged from 5 to 13. All patients were instructed to empty the bladder before simulation and before each treatment fraction. At the beginning of the study a rectal enema was prescribed to all patients before simulation and before each treatment to reduce interfraction and intrafraction target motion. Later on, rectal purging was restricted to patients with medium to large rectal volumes at simulation (ie, >60 mL). In BCN, the first 22 patients were simulated and treated by the use of an endorectal balloon (ERB) inflated with 60 mL of air after purging the rectum as part of a study aiming to optimize internal organ motion reduction. The treatment plans were generated from a single CT scan in all patients treated in GVA (n = 38) and in 58 patients treated in BCN. All remaining patients treated in BCN underwent a second replanning CT scan for the last 4 fractions to assess for potential changes in rectal volume occurring during irradiation. Rectal and bladder dosimetric results for the 2 treatment schedules planned on a single CT scan (n = 96) are summarized in Table 2.

The treatment verification was performed with the use of an offline treatment verification protocol, and appropriate patient repositioning was made with bone matching on portal images with no image-guided radiation therapy (IGRT) support. In GVA, weekly CTs were performed only for patients with large rectal volumes at simulation (>60 mL). All patients in BCN underwent a weekly repositioning control CT scan before treatment (ie, every second fraction) to control for prostate motion and stability of the rectal and bladder volumes. CTV displacements $\geq$1 cm were corrected by replanning the treatment and controlling closely for rectal purging and/or for ERB insertion and inflation before every fraction.

While receiving treatment, patients were reviewed once weekly followed by a medical visit 6 to 8 weeks after treatment completion, then every 3 months during the first year and every 6 months thereafter. The follow-up visits involved measurement of prostate specific antigen (PSA), a digital rectal examination, and an assessment of the gastrointestinal (GI) and genitourinary (GU) toxicities, which were scored according to the Common Terminology Criteria for Adverse Events version 3.0 grading scales. Late toxicity was defined as any side effect after 90 days from completion of treatment. Biochemical failure was defined according to the Phoenix consensus criteria (PSA nadir + 2 ng/mL). Local failure was confirmed by either prostate biopsies, 18F-choline/C11-acetate positron emission tomography (PET)-CT imaging, or both. The median follow-up times were 80.2 months (range, 4.5-121.0 months) and 56.5 months (range, 1.4-91.2 months) for patients treated to 56 and 60 Gy, respectively.

Forty-three (26.4%) patients received neoadjuvant and concomitant androgen deprivation therapy (ADT) for 6 months if they were classified in the National Comprehensive Cancer Network (NCCN) intermediate-risk group or neoadjuvant, concomitant, and then adjuvant ADT for 9 months if they belonged to the NCCN high-risk group.

Table 2 Dosimetric results for rectum and bladder based on the 2 treatment schedules in patients undergoing a single planning computed tomographic scan (% of patients respecting the planning dose constraints*) (n = 96)

	Rectum, DVH (%)			Bladder, DVH (%)		
Dosimetric variable	56 Gy (n = 28)	60 Gy (n = 68)	*P* value	56 Gy (n = 28)	60 Gy (n = 68)	*P* value
$V_{29Gy\ (\sim V50\%)}$	53.8 (39.3%)	52.2 (33.8%)	.455	60.8 (29.6%)	56.1 (36.8%)	.195
$V_{36Gy\ (V50Gy\ NTD2Gy)}$	40.5	40.7	.934	49.6	45.1	.221
$V_{50Gy\ (V70Gy\ NTD2Gy)}$	15.8 (96.4%)	20.9 (91.2%)	.001	28.7 (57.1%)	26.4 (61.8%)	.444
$V_{54Gy\ (V75Gy\ NTD2Gy)}$	4.2 (100%)	13.8 (100%)	.0001	17.5 (89.3%)	20.7 (86.8%)	.221
$V_{56Gy\ (V78.4\ Gy\ NTD2Gy)}$	0.4	9.6	.0001	5.2	17.1	.0001
$V_{60Gy\ (V84\ Gy\ NTD2Gy)}$	0	1.3	.0001	0.3	3.6	.0001

Abbreviations: DVH = dose-volume histogram; NTD_{2Gy} = normalized total dose 2 Gy assuming an α/β ratio of 3 Gy for late reactions; Vx % = percentage of volume receiving x% of the dose; Vx = percentage of volume receiving x dose; V_{xGy} = volume in percentage of rectum or bladder receiving more than x Gy.

* Planning dose constraints: Rectum and bladder: V50% $\leq$ 50% (V50% of 56 Gy = V28 Gy//V50% of 60 Gy = V30 Gy); V90% $\leq$ 30% (V90% of 56 Gy = V50 Gy//V90% of 60 Gy = V54 Gy).

Table 3 Acute genitourinary and gastrointestinal toxicities (n = 163)

	Genitourinary		Gastrointestinal	
Grade*	56 Gy	60 Gy	56 Gy	60 Gy
0	24 (29.6)	24 (29.6)	52 (64.2)	41 (60.0)
1	29 (35.8)	34 (42.0)	19 (23.5)	30 (36.6)
2	28 (34.6)	20 (24.7)	10 (12.3)	11 (13.4)
3	-	3 (3.7)	-	-
4	-	-	-	-

* Common Terminology Criteria for Adverse Events version 3.0.

Neoadjuvant ADT started 2 months before radiation therapy, beginning with bicalutamide 50 mg daily for only 30 days and followed 10 to 15 days after the start of bicalutamide with a 3-month slow-releasing LH-RH analogue. As shown in Table 1, a significantly larger proportion of patients treated with 60 Gy received ADT (31/82 patients) compared with those treated with 56 Gy (12/81 patients).

Statistical analysis was carried out with the SPSS statistical package (IBM SPSS Statistics version 22). Demographic and patient characteristics were compared by means of Student *t* test and the Mann-Whitney *U* test for continuous variables. Pearson's χ^2 test and Fisher test were used to compare categorical data. To assess 5-year survival outcomes for late toxicity, biochemical failure, local and distant metastases, and overall survival, Kaplan-Meier estimates were calculated with the corresponding survival curves. Multivariate regression analyses were performed to identify potential factors contributing to biochemical failure (age, NCCN risk group, ADT, radiation therapy dose).

Results

All patients completed treatment with no interruptions. During the course of the treatment, 39% of the patients reported grade 1 urinary symptoms and 29% reported grade 2 urinary toxicity, which was treated with α-1 blockers, nonsteroidal anti-inflammatory drugs, or both, and 30% and 13% described symptoms of grade 1 and 2 GI toxicities, respectively. At 6 weeks the majority of patients did not experience any GU or GI toxicity (76% and 85%, respectively) (Table 3). There were no statistically significant differences with regard to the urinary and GI toxicities for the 2 dose groups, either during treatment (GU toxicity, $P = .193$; GI toxicity, $P = .149$) or at the first follow-up assessment 6 weeks after completion ($P = .126$ and $P = .224$, respectively).

As shown in Figure 1a, the 5-year probability of grade ≥2 GU toxicity-free survival was 96 ± 2.3% for patients treated in the 56-Gy group and 78.2 ± 5.1% for those treated in the 60-Gy group ($P = .001$). By contrast, there was no difference in the 5-year grade ≥3 GU toxicity-free survival between the 56-Gy and 60-Gy groups (97.1 ± 2% vs 93.4 ± 3% respectively, $P = .33$). The commonest grade ≥2 symptom was macroscopic hematuria, followed by dysuria, and only 1 patient treated with 56 Gy experienced grade 4 urinary toxicity (urinary retention) (Table 4).

As shown in Figure 1b, the 5-year probability of grade ≥2 GI toxicity-free survival was 98.6 ± 1.3% for patients treated in the 56-Gy group and 85.1 ± 4.5% for those treated in the 60 Gy group ($P = .005$). The 5-year grade ≥3 GI toxicity-free survival was 98.6 ± 1.3% for patients treated in the 56-Gy group and 90 ± 4% for those treated in the 60-Gy group ($P = .03$). The commonest observed toxicity was rectal bleeding. Table 2 shows the dosimetric results for rectum and bladder for 96 patients having undergone a single planning CT, for each treatment group. The recommended dose constraints were respected for most patients in both treatment groups. However, the mean percentage volumes of rectum receiving more than 50 Gy ($V50_{Gy}$, equivalent to $V70_{Gy}$ $NTD2_{Gy}$, $\alpha/\beta = 3$ Gy) were 15.8% and 20.9% for the 56-Gy and 60-Gy groups, respectively ($P = .001$); the mean $V56_{Gy}$ to the bladder was 5.2% and 17.1% of the volume, for the 56-Gy and 60-Gy groups, respectively ($P = .0001$). As also shown in Table 2, the median value for the whole group of patients regarding $V50_{Gy}$ was 19% of the rectal volume (similar to the validated $V50_{Gy} < 20\%$ in QUANTEC) (22). Dividing our patients into 2 groups above or below this dose constraint, we observed that a $V50_{Gy} > 19\%$ or $\leq 19\%$ correlated with a 5-year grade ≥2 late GI toxicity-free survival of 80.8 ± 6.3% and 95.3 ± 3.2%, respectively ($P = .031$). Furthermore, regarding the highest doses received by the rectum, a trend for a reduced grade ≥2 rectal toxicity in patients with a $V56_{Gy} \leq 10\%$ ($V78.4_{Gy}$ $NTD2_{Gy}$, $\alpha/\beta = 3$ Gy) was observed. Indeed, the 5-year grade ≥2 GI toxicity-free survival was 92.2 ± 3.4% and 73.2 ± 10.7% for a $V56_{Gy} \leq 10\%$ and a $V56_{Gy} > 10\%$, respectively ($P = .064$).

Patients treated with a dose of 56 Gy and 60 Gy experienced 5-year biochemical progression-free survival (bPFS) of 80.9 ± 4.6% and 93.3 ± 3.9%, respectively ($P = .007$) (Fig. 2). On multivariate regression analysis, the only variable that correlated significantly with biochemical failure was a lower radiation therapy dose ($P = .016$, hazard ratio = 4.58, 95% confidence interval 1.33-15.8) (Table E1; available online at www.redjournal.org). Of the 22 patients who experienced biochemical relapse, 12 relapses were local recurrences only, 2 were distant only, and 3 were both local and distant. Local and distant failures were confirmed by 18F-choline/C11-acetate PET-CT imaging, biopsies, or both. Despite these investigations, for 5 patients the exact failure site was not identified.

The 5-year local failure-free and distant metastases-free survival figures for the 56-Gy and 60-Gy treatment groups have been 87.5 ± 3.9% and 96.2 ± 2.7%, $P = .10$ and 95.3 ± 2.6% and 100%, $P = .07$, respectively. Only 2 patients have died so far (1 death in each dose group): 1

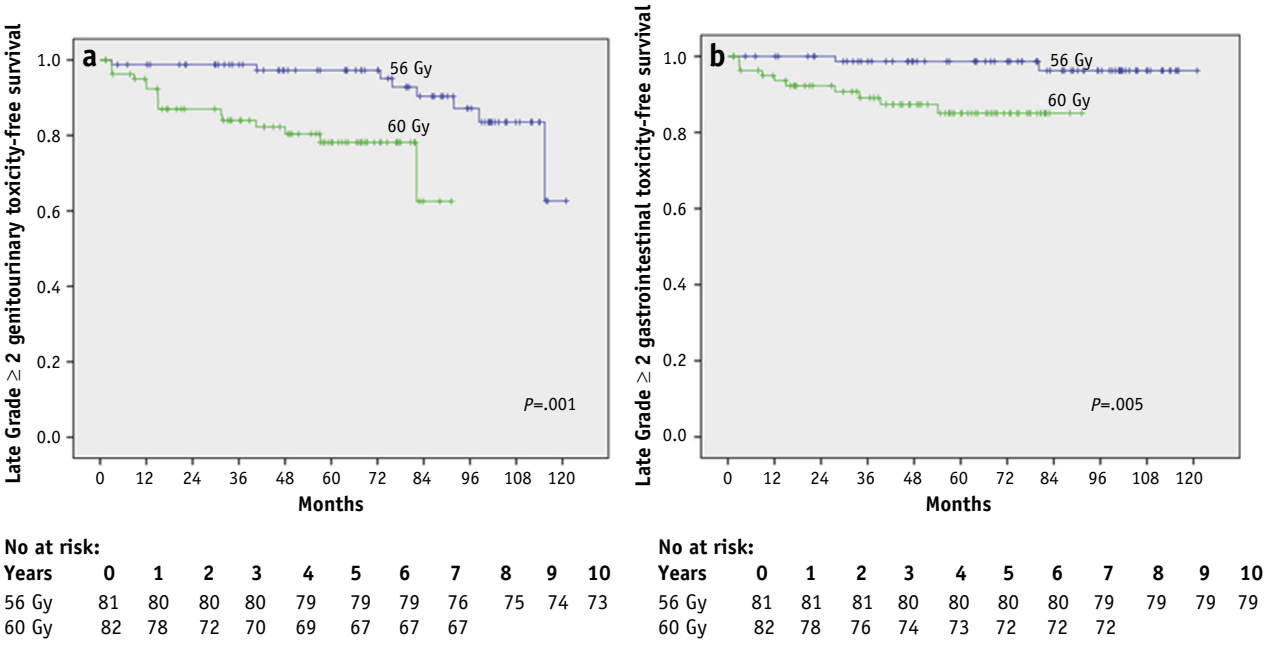

Fig. 1. Late grade ≥2 genitourinary (a) and gastrointestinal (b) toxicity-free survival in patients treated with 56 Gy versus 60 Gy.

resulting from complicated urinary sepsis secondary to prostate cancer and the other resulting from renal failure while the patient was in cancer remission.

Discussion

This nonrandomized retrospective assessment suggests that men with clinically localized prostate cancer and a relatively low risk for nodal metastases treated with 60 Gy in 4-Gy fractions are more likely to be free of biochemical failure in 5 years than are patients treated with 56 Gy in 4-Gy fractions. This advantage, however, is obtained against a tradeoff of increased late toxicity in the high-dose group (ie, ≈3x for urinary and ≈10x for GI ≥ grade 2 toxicity).

These results add further evidence to what has already been shown by several retrospective and prospective dose-escalation standard fractionated trials showing an improved 5-year bPFS rate with dose escalation against a higher risk of toxicity (4-7, 23). The dose threshold above which no gain in biochemical tumor control is observed has been suggested to be likely between 84 and 90 Gy (24-26). Hypofractionated regimens may thus be advantageous, assuming a low α/β ratio for prostate cancer cells (15, 16, 18, 27, 28), with the present study suggesting a clinical benefit when the dose is escalated (NTD_{2Gy}) from 88 to 94 Gy. However, the largest phase 3 trial by Pollack et al (16), with a median follow-up time of 68.4 months, showed that hypofractionated radiation therapy of 70.2 Gy in 26

Table 4 Late genitourinary and gastrointestinal toxicities (n = 163)

	Genitourinary		Gastrointestinal	
Grade*	56 Gy	60 Gy	56 Gy	60 Gy
0	57 (70.4)	51 (62.2)	61 (75.3)	50 (61.0)
1	15 (18.5)	16 (19.5)	19 (23.5)	23 (28.0)
2	7 (8.6)	12 (14.6)	-	4 (4.9)
3	1 (1.2)	3 (3.7)	1 (1.2)	5 (6.1)
4	1 (1.2)	-	-	-

* Common Terminology Criteria for Adverse Events version 3.0.

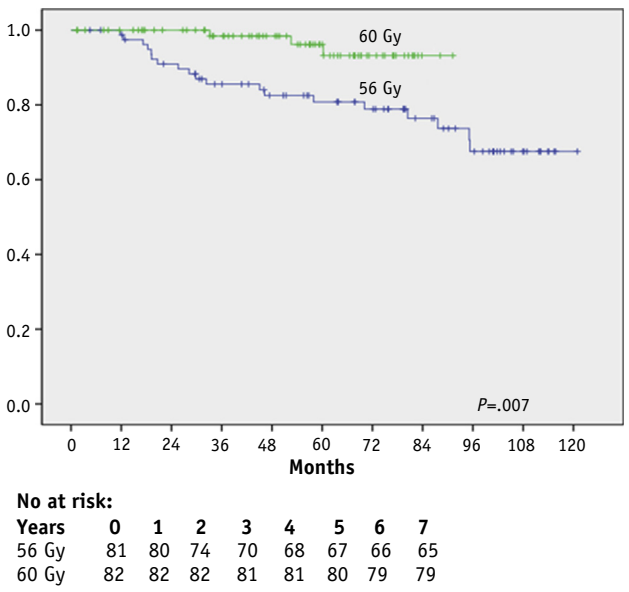

Fig. 2. Kaplan-Meier actuarial curves showing the biochemical progression-free survival of patients treated with 56 Gy and 60 Gy.

fractions (84.4 Gy NTD_{2Gy}) did not confer a benefit in bPFS compared with a normofractionated schedule of 76 Gy in 38 fractions.

The treatment setup of patients reported in this study was done without IGRT support, though monitored with offline corrected weekly CT scans. The wide CTV-to-PTV margins of 6 to 10 mm might be in part the reason for a higher toxicity rate in the high-dose group. Nevertheless, patients treated with 56 Gy experienced almost optimal 5-year ≥ grade 2 urinary and GI toxicity rates of less than 5% despite the generous margins surrounding the CTV.

The protracted hypofractionated schedule with 2 weekly fractions (8 Gy/week) prolonging the OTT may explain the low acute toxicity observed among all patients. However, excessive protraction may also have a negative effect on tumor control as a consequence of accelerated tumor cell repopulation in fast-growing neoplasms such as ear, nose, and throat tumors and tumors of the lung and bladder. Prostate cancer has been for years considered a slow-growing tumor with a negligible cell repopulation during the first 8 to 9 weeks of standard fractionated radiation therapy (29, 30), for which OTT was not considered a biologically limiting factor. Thus, delivering 56 and 60 Gy in 6.5 and 7 weeks was chosen to favor tolerance. This approach is unique because it contrasts with the shorter OTT of 4 to 5 weeks for most hypofractionated treatment schedules reported so far.

Recent studies have suggested, however, a clinically significant repopulation effect in patients with low-risk and intermediate-risk prostate cancer with an accelerated repopulation occurring at 4 to 5 weeks and an effective clonogen doubling time of 12 days (31, 32). For these patients, an OTT longer than 5 to 6 weeks may influence the outcome, especially if they are treated with suboptimal doses. An OTT longer than the lag-time for an accelerated repopulation of clonogenic cells may artifactually increase the α/β value of prostate cancer cells from 1.5 Gy (95% CI, 0.9-2.2 Gy) to 4 Gy (95% CI, 2.1-6.3 Gy) as reported by Miralbell et al (17). According to the above rationale, 56 Gy (14 × 4 Gy) delivered in 6.5 weeks, and considering an "artifactual" $\alpha/\beta = 3$ to 4 Gy, would drop the NTD_{2Gy} from 88 Gy to 78 to 74 Gy, more in agreement with the 80% 5-year bPFS reported in this study (7). This hypothesis is probably supported by the better long-term bPFS results observed delivering similar NTD_{2Gy} doses but in a shorter OTT with stereotactic body radiation therapy (SBRT) techniques (Table 5) (33-38). Nevertheless, it remains unanswered whether the promising disease control rates obtained with SBRT compared with those in our series can be explained by the shorter OTT only, by the use of modern repositioning techniques, or by the combination of both of them.

Since 2010, and keeping all of the above in mind, we decided to change from 60 to 56 Gy though reducing the OTT from 6 to 7 weeks (4 Gy twice a week) to 4 to 5 weeks (4 Gy, three times a week). By doing so we expected to be in the safe lag-time interval before the start of accelerated repopulation, thus improving the outcome to the corresponding NTD_{2Gy} of 88 Gy while keeping the toxicity to at least as low as presented in this report for the patients treated with 56 Gy.

On the other hand, the marked differences in $V50_{Gy}$ between the 2 treatment groups (Table 2) might also be a strong argument to consider alternative methods to improve toxicity rates by lowering the dose to the rectum (ie, $V50_{Gy}$ to less than 20% of the rectal wall), the bladder, and the urethra without reducing the prescription dose of 60 Gy, that proved to be optimal concerning bPFS. Indeed, IGRT,

Table 5 Hypofractionated treatment schedules with corresponding biochemical progression-free survival rates and late GU and GI toxicity rates

Study	Daily Fx (Gy)	Total dose (Gy)	NTD_{2Gy} α/β ratio 1.5 Gy	OTT (weeks)	FU (mo)	Technique	5-year bPFS (%)	≥G2 GU toxicity (%)	≥G2 GI toxicity (%)
Chen et al (33)	7	35	85	1.5	27.6	SBRT	99†	31	1
	7.25	36.25	90						
King et al (36, 38)	7 - 9.75	36.25*	85-125.4	1-1.5	36	SBRT	93	0	0
Loblaw et al (37)	7	35	85	4	55	SBRT	98	1	1
Kang et al (34)	8-9	32-36	88.5-110.1	1	40	SBRT	93.6	6.8	11.4
Katz et al (35)	7	35	85	1.5	60	SBRT	97‡	15	7
	7.25	36.25	90				90.7§		
							74.1‖		
Present study	4	56	88	6.5	67.7	IMRT/	80.9	4	1.4
	4	60	94	7		DAT	93.3	21.8	14.9

Abbreviations: bPFS = biochemical progression-free survival; DAT = dynamic arc therapy; Fx = fraction, GI = gastrointestinal; GU = genitourinary; IMRT = intensity modulated radiation therapy; NTD_{2Gy} = normalized total dose (Gy); OTT = overall treatment time; SBRT = stereotactic body radiation therapy.

* Median dose (range, 35-40 Gy) over 5 fractions for 84% of patients and a median dose of 39 Gy in 4 fractions for the remainder.

† 2-year actuarial rate.

‡ Low-risk patients.

§ Intermediate-risk patients.

‖ High-risk patients.

the use of ERB and intraprostatic fiducial markers, and implanting reabsorbable spacers between the prostate and the rectum resulted in reducing the CTV-to-PTV expansion to 3 mm from the former 6 to 10 mm, thus minimizing the irradiation of the rectum and bladder. In addition, a simultaneous dose reduction to the urethra while delivering the full prescribed dose to the target may also be possible with an optimized dosimetry using intensity modulated techniques, thus potentially reducing GU toxicity as well.

In conclusion, the 5-year treatment outcome and associated urinary and GI toxicity of 2 moderate hypofractionated dose escalation treatment regimens showed that an additional single fraction of 4 Gy, in patients with clinically localized prostate cancer treated with a hypofractionated IMRT schedule of 14 $\times$ 4 Gy, over 6.5 weeks, resulted in a clinical advantage at the cost of an increased rate of long-term side effects. Further improvements in the therapeutic ratio are expected for the high-dose approach with the delivery of contemporary EBRT in $<$5 weeks using a stricter dose optimization, IGRT repositioning techniques, and smaller PTV margins.

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