Journal of Cancer Research and Clinical Oncology (2019) 145:1581–1588
https://doi.org/10.1007/s00432-019-02893-4

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Twice- vs. thrice-weekly moderate hypofractionated radiotherapy for prostate cancer: does overall treatment time matter?

Vérane Achard[1] · Sandra Jorcano[2] · Michel Rouzaud[1] · Lluís Escudé[2] · Raymond Miralbell[1,2] · Thomas Zilli[1]

Received: 13 January 2019 / Accepted: 12 March 2019 / Published online: 18 March 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Purpose To evaluate the influence of overall treatment time (OTT) in disease control, acute, and long-term side effects with moderate hypofractionated external beam radiotherapy (RT) for prostate cancer (PCa) delivered either twice- or thrice-a-week.

Methods 157 patients with localized PCa were treated consecutively with 56 Gy in 4 Gy/fraction delivered either twice (86 patients, from 2003 to 2010, group-1) or thrice a week (71 patients, from 2010 to 2017, group-2) using IMRT or VMAT techniques. Gastrointestinal (GI) and genitourinary (GU) toxicities were scored according to the CTCAE v3.0 grading scale. Median follow-up was 110 and 56 months for groups 1 and 2, respectively.

Results At 6 weeks, patients treated thrice-a-week experienced higher acute ≥ grade-2 GU toxicity compared to those treated twice a week (25.4% vs 5.8%, $p=0.001$) even though none presented ≥ grade-3 GU or GI toxicity in the thrice-a-week group. The 5-year ≥ grade-2 late GU toxicity-free survival was higher in group-1 (95.9 ± 2.3%) than in group-2 (81.5 ± 4.9%, $p=0.003$), while no differences in ≥ grade-2 late GI toxicity-free survival were observed between both groups (97.5 ± 1.7% vs. 97 ± 2.1% for groups 1 and 2, respectively). The 5-year biochemical relapse-free survival (bRFS) was not different for patients treated twice compared to those treated thrice-a-week (80.6 ± 4.5% vs. 85.3 ± 4.8%, respectively, $p=0.441$), as much as for patients treated in > 5 weeks vs. those treated in ≤ 5 weeks (81.3 ± 4.4% vs. 84.4 ± 5.1%, respectively, $p=0.584$).

Conclusions In this retrospective hypothesis-generating analysis, less vs. more than 5 weeks OTT may increase acute and late GU toxicities without significantly improving bRFS in patients treated to high effective doses (> 80 Gy) with moderate hypofractionated RT. Prospective trials evaluating the impact of OTT on hypofractionated schedules for PCa are warranted.

Keywords Prostate cancer · Hypofractionation · Overall treatment time · Radiotherapy · Toxicity

Introduction

Moderate hypofractionated external beam radiation therapy (EBRT) has been proposed in the last few years as an alternative to standard fractionation for prostate cancer. Indeed, reports on non-inferiority phase III randomized trials have shown comparable results regarding outcome and toxicity with either fractionated regimens (Dearnaley et al. 2016; Incrocci et al. 2016; Lee et al. 2016).

In fast growing tumors, a protracted overall treatment time (OTT) may be detrimental for tumor control due to accelerated repopulation of surviving clonogenic tumor cells (Withers et al. 1988; Perez et al. 1995; Murphy et al. 2016; Koukourakis et al. 1996; Graf et al. 2003). For prostate cancer, an alleged slowly growing cancer, the impact of OTT remains an open and unresolved issue (Haustermans et al. 1997). Although a too long OTT (e.g., > 9 weeks) may have a detrimental effect on long-term disease control with conventional fractionation, the impact of OTT on outcome has never been specifically explored in the setting of moderated hypofractionation regimens for prostate cancer. Furthermore, changes in dose per fraction and OTT have shown to impact treatment tolerance as a consequence of healthy tissue repair and cell repopulation during the acute phase. This may also interfere with the healing process and determine, later on, different degrees of late toxicity severity.

Since 2003, patients with localized prostate cancer and a reduced risk of pelvic nodal involvement [i.e., ≤ 20%, Roach index (Roach et al. 1994)] were treated with moderate

✉ Thomas Zilli
Thomas.Zilli@hcuge.ch

[1] Radiation Oncology Division, Geneva University Hospital, 1211 Geneva 14, Switzerland

[2] Radiation Oncology, Teknon Oncologic Institute, Barcelona, Spain

hypofractionation delivering 56 Gy in 4 Gy/fractions, twice weekly. We assumed at that time that accelerated repopulation of prostate cancer cells might be marginal at least during the usual 7 weeks of treatment (Kountouri et al. 2016; Zilli et al. 2011). In 2010, however, several reports suggested that, indeed, tumor cell repopulation, especially in low- and intermediate-risk tumors, might be significant with OTTs longer than 4–5 weeks (Miralbell et al. 2012; Thames et al. 2010). Considering this, we decided to reduce the OTT from 7 to less than 5 weeks (i.e., 14 × 4 Gy/fraction delivered thrice instead of twice weekly).

In this study, we aimed to evaluate retrospectively the toxicity and outcome of patients bearing prostate cancer with low metastatic potential treated with the same dose (56 Gy in 14 fractions) but two different fractionation regimens: twice vs. thrice weekly.

Materials and methods

From 2003 to 2017, a total of 157 patients with localized prostate cancer were sequentially treated in two associated institutions (Geneva, $n = 44$ and Barcelona, $n = 113$) with curative EBRT using a moderate hypofractionated schedule. Patients included in this study were clinically staged cT1c to cT3a cN0 cM0 (2010 American Joint Committee on Cancer staging system) with a lymph node risk of ≤ 20% (Roach et al. 1994). All patients underwent a digital rectal examination (DRE) and pretreatment prostate-specific antigen (PSA) determination. Multiparametric contrast-enhanced pelvic magnetic resonance imaging (MRI) was performed at diagnosis in 140 (89%) of 157 patients and bone scans were performed in patients with a Gleason score (GS) of 7, a PSA level > 10 ng/mL, or both.

Patient and tumor characteristics are described in Table 1. Except for the GS, the two fractionation groups were well balanced with no differences regarding the patients' prognostic characteristics. Differences in GS values between groups may be explained by the inverse-stage migration phenomenon with higher GS observed in recent years (Leyh-Bannurah et al. 2018).

From 2003 to 2010, 86 patients (54.8%) were treated twice weekly with 56 Gy in 4 Gy/fraction (14 × 4 Gy) and a median OTT of 46 days (range 38–90 days). Since 2010 throughout 2017, the same fractionation schedule was delivered thrice weekly to 71 patients (45.2%) and a median OTT of 30 days (range 29–40). Assuming an α/β value for prostate cancer of 1.2 Gy (Vogelius and Bentzen 2018), the two groups received an equivalent normalized total dose in 2 Gy/fraction ($NTD_{2\,Gy}$) of 91 Gy. However, considering an OTT-based increase of α/β to 2.7 Gy if 0.31 Gy are lost daily (Vogelius and Bentzen 2018), the corresponding equivalent $NTD_{2\,Gy}$ for the two fractionation regimens were 82.5 Gy and 87.4 Gy for the twice- and the thrice-weekly schedules, respectively.

Table 1 Patient and tumors characteristics ($n = 157$)

Characteristics	2×/weekly	3×/weekly	*p*-value
Patients [*n* (%)]	86 (54.7)	71 (45.2)	
Age (years)			
Median (range)	68 (51.2–86)	71 (47.9–82.4)	0.121
PSA at diagnosis (ng/ml)			
Median (range)	7.8 (1.5–30)	8.3 (1.2–25.3)	0.185
< 10	70 (81.3)	47 (66.1)	
10–20	15 (17.2)	20 (28.6)	
≥ 20	1 (1.1)	4 (5.7)	
AJCC cT stage			
Tx	1 (1.1)	–	0.760
T1	41 (47.6)	33 (46.4)	
T2	30 (34.5)	21 (30)	
T3a	14 (16.1)	17 (24.3)	
NCCN risk group (MRI based for T3)			
Low	14 (16.3)	5 (7)	0.089
Intermediate	45 (52.3)	34 (47.9)	
High	27 (31.4)	32 (45.1)	
Gleason score			
≤ 6	57 (75)	20 (29)	0.0001
7	29 (33.7)	51 (71.8)	

ADT androgen deprivation therapy, *AJCC* American Joint Committee on Cancer, *MRI* magnetic resonance imaging, *NCCN* National Comprehensive Cancer Network, *PSA* prostate-specific antigen

Patients were treated to the prostate and seminal vesicles (SV) if the estimated risk of SV invasion was > 15% (Diaz et al. 1994). Intensity-modulated radiotherapy (IMRT, $n = 130$), dynamic arc ($n = 4$), or volumetric-modulated arc (VMAT, $n = 23$) techniques were used (Zilli et al. 2011; Kountouri et al. 2016). Image-guided techniques evolved over years from an offline treatment verification protocol with bone matching on portal images in the early years to the use of intra-prostatic fiducials and cone-beam CT with soft-tissue matching. While in the majority of the patients (92%) treated in the twice-weekly group daily repositioning was performed with bone matching on portal images, fiducial markers and/or cone-beam CT were used for image guidance in all patients treated thrice weekly. In both institutions, for patients treated in the twice-weekly group, prostate motion and stability of rectum and bladder volumes were verified with a weekly repositioning control CT scan undertaken before every second fraction (Barcelona) or only in patients with rectal volumes > 60 cc at simulation (Geneva) (Kountouri et al. 2016; Zilli et al. 2011).

Neo-adjuvant and concomitant androgen deprivation therapy (ADT) was given for 6 months to intermediate-risk patients and at least 9 months of additional adjuvant ADT

for high-risk patients. ADT preceded by 2–3 months EBRT. The usual regimens consisted of oral bicalutamide 50 mg q.d. for 30 days and subcutaneous or intra-muscular injections of slow-releasing LH-RH analogs every 3 months. A larger proportion of patients treated thrice weekly received ADT (47/71 patients, 67%) compared with those treated twice weekly (14/86 patients, 16%) ($p < 0.001$).

Status-check visits were done once a week during the treatment period. Follow-up visits, started 6 weeks after treatment completion, were performed every 4 months during the first year and every 6 months thereafter. PSA measurement, digital rectal examination, and toxicity evaluation were assessed at each visit by the attending physician. Acute (up to 3 months after RT completion) and late genitourinary (GU) and gastrointestinal (GI) toxicity were assessed using the Common Terminology Criteria for Adverse Events version 3.0 grading scale. Biochemical failure was defined according to the Phoenix consensus criteria (PSA nadir + 2 ng/ml) (Roach et al. 2006). Local failures were confirmed by either prostate biopsies, 18F-choline/C11-acetate positron-emission tomography (PET)/CT imaging, or both. The follow-up period for the whole cohort was 67 months (range 1.5–172). Patients treated twice weekly had a longer follow-up (median of 110 months, range 4.5–172) compared to the thrice times a week group (median of 56 months, range 1.5–91).

GU and GI late toxicity-free and biochemical relapse-free survival rates (bRFS) with standard deviations were estimated using the Kaplan–Meier method, with the log-rank method to compare groups. Multivariate regression analyses were performed to identify potential factors contributing to biochemical failure (NCCN risk classes, Gleason score $\leq 3+4$ vs. $4+3$, PSA at diagnosis, ADT use, and median OTT ≤ 42 vs. > 42 days). Demographic and patient characteristics were compared by means of Student's *t*-tests for continuous variables. Chi-square test and Fisher test were used to compare categorical data. Statistical significance was defined as p-value ≤ 0.05. All analyses were performed using the SPSS statistical package (IBM SPSS statistics version 22). The study was approved by the local ethical committee (Commission cantonale d'éthique de la recherche CCER, project number 2018-00614).

Results

Acute toxicity

All patients completed treatment without interruptions. Acute toxicity scores are summarized in Table 2. At RT completion, patients treated thrice weekly presented with a higher rate of grade-2 GU side effects compared to patients treated bi-weekly (47.9% vs. 32.6%, respectively). Grade-2 GU toxicity was mostly managed with $\alpha - 1$ blockers, non-steroidal anti-inflammatory drugs, or both. Only one case of grade-3 GU toxicity was observed in the twice weekly group. Six weeks after RT completion, patients treated thrice a week also presented with a higher rate of grade-2 GU toxicity compared with patients treated twice a week (25.4% vs. 5.8%, $p = 0.001$).

No differences were observed between the two fractionation groups at the end of RT regarding GI toxicity. Grade-3 or more GI events have never been reported. Six weeks after RT grade-2 toxicity was < 3% in both groups.

Late toxicity

No differences in 5-year toxicity-free survival were observed in grade 3 or more GU toxicity between both groups ($95 \pm 4.9\%$ vs. $94.7 \pm 5.1\%$ for patients treated 2×- vs. 3×

Table 2 Acute genitourinary (GU) and gastrointestinal (GI) toxicities at the end of EBRT (2A) ($n = 157$) and at 6 weeks after EBRT (2B) ($n = 156$)

Grade[a]	GU		*p*-value	GI		*p*-value
	2×/week	3×/week		2×/week	3×/week	
(a)						
0	23 (26.7%)	11 (15.5%)	0.139	54 (62.8%)	37 (52.1%)	0.119
1	34 (39.5%)	26 (36.6%)		21 (24.4%)	28 (39.4%)	
2	28 (32.6%)	34 (47.9%)		11 (12.8%)	6 (8.5%)	
3	1 (1.2%)	–		–	–	
4	–	–		–	–	
(b)						
0	66 (76.7%)	37 (52.1%)	0.001	78 (90.7%)	61 (85.9%)	0.586
1	15 (17.4%)	15 (21.1%)		6 (7.0%)	8 (11.3%)	
2	5 (5.8%)	18 (25.4%)		2 (2.3%)	1 (1.4%)	
3	–	–		–	–	
4	–	–		–	–	

[a]Common Terminology Criteria for Adverse Events version 3.0

per week, respectively, $p = 0.986$). On the contrary, the 5-year ≥ grade 2 late GU toxicity-free survival was higher in group-1 (95.9 ± 2.3%) compared to group-2 (81.5 ± 4.9%, $p = 0.003$) (Fig. 1). Late GU toxicity mostly consisted of obstructive symptoms, urgency, and macrohematuria. As far as GI toxicity is concerned, no differences in 5-year ≥ grade-2 GI toxicity-free survival rates were observed between patients treated twice a week vs. patients treated thrice weekly (97.5 ± 1.7% vs. 97 ± 2.1%, $p = 0.766$). The most common GI ≥ grade-2 toxicity was rectal bleeding.

Outcome

Thirty-two patients presented with a biochemical failure (24 and 8 patients in the twice- and thrice-weekly groups, respectively). The 5-year bRFS rates for patients treated twice and thrice weekly were 80.6 ± 4.5% and 85.3 ± 4.8%, respectively ($p = 0.441$) (Fig. 2). None of the covariates evaluated for a potential correlation with biochemical failure reached a statistical significance on multivariate Cox analysis. By stratifying patients based on OTT, the 5-year bRFS remained similar in patients treated in > 5 weeks (81.3 ± 4.4%) vs. patients treated in ≤ 5 weeks (84.4 ± 5.1%) ($p = 0.584$) (Fig. 3).

The 5-year local failure-free and distant metastasis-free survival figures for the twice- and thrice-weekly treatment groups were 86.7 ± 4.0% vs. 94.1 ± 3.3% ($p = 0.120$) and 95.8 ± 2.4% vs. 85 ± 5.3% ($p = 0.121$), respectively. At last follow-up, 13 out of 157 patients passed away. The cause of death was unknown in three patients though was unrelated to prostate cancer in nine. One patient died from a septic shock secondary to a urinary infection in a post-radiation atonic bladder with ureteral reflux. The 5-year overall survival rate for the whole cohort was 97.3 ± 1.5%.

Discussion

Although there are studies that suggest the existence of clinically significant tumor cell repopulation in low-risk and intermediate-risk prostate cancers (with a 4–5-week lag-time and an effective clonogen doubling time of 12 days) (D'Ambrosio et al. 2008; Gao et al. 2010), we have been unable to show any significant difference in the outcome after delivering the same dose with different OTTs. As expected, we observed, however, that a more protracted OTT was associated with better recovery from acute toxicity and higher long-term GU toxicity-free survival figures. Results of our series are noteworthy because to our knowledge this is the first attempt to investigate the question of OTT with two hypofractionated RT regimens differing exclusively in the weekly number of fractions though delivering the same total dose and dose/fraction.

The influence of OTT has been and still is a controversial issue. In the 1990s, unlike Lai et al., who did not observe any correlation between OTT and outcome, Amdur et al., reported worse local control rates with OTT of ≥ 8 weeks compared to patients treated in < 8 weeks (Amdur et al.

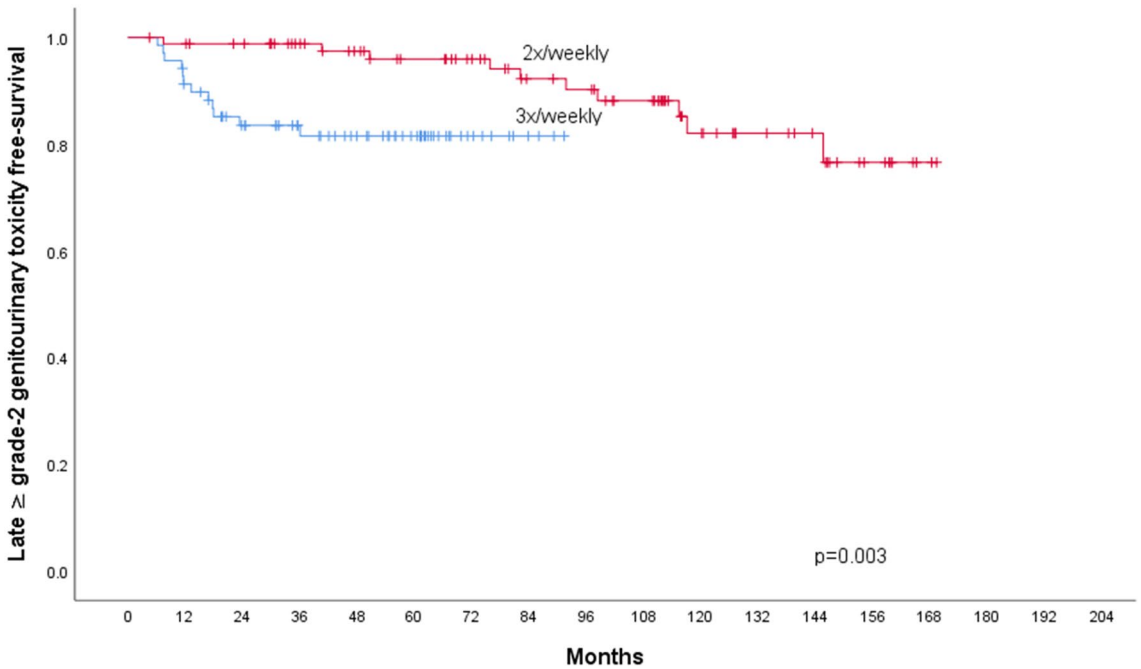
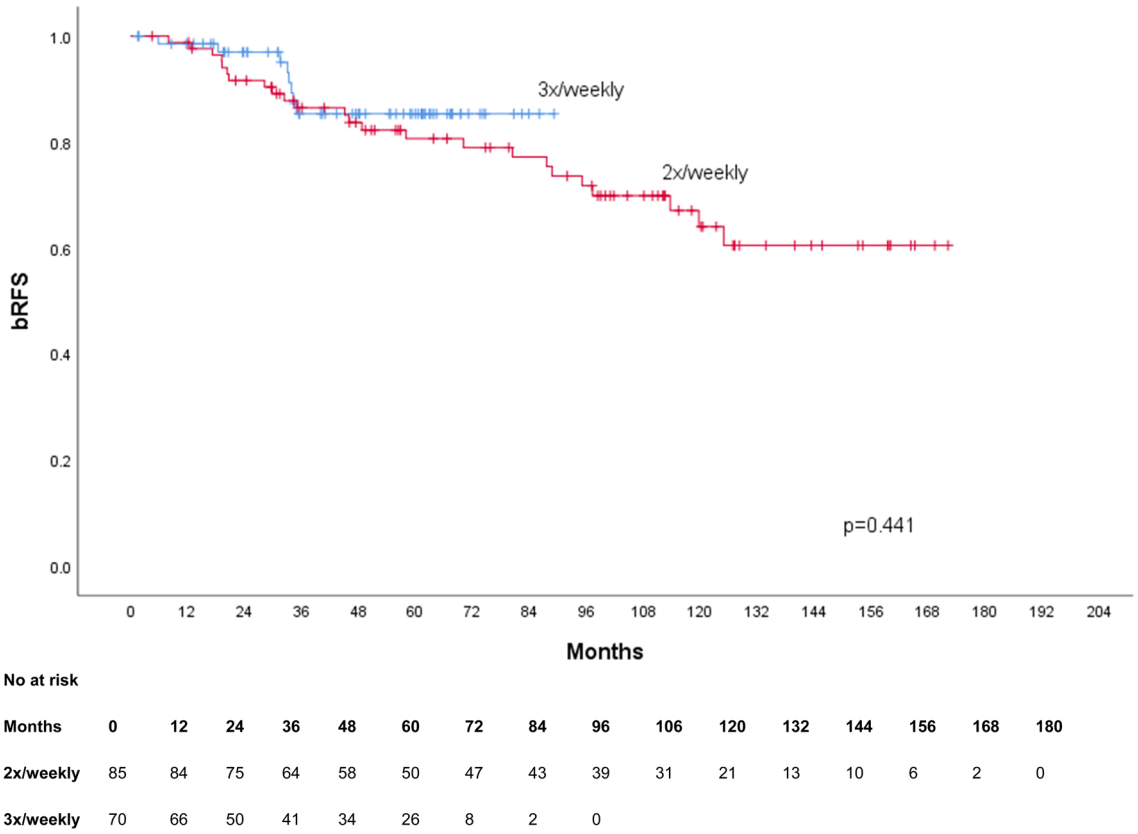


Fig. 1 Late grade ≥ 2 genitourinary toxicity-free survival for patients treated twice weekly vs. thrice weekly



No at risk																
Months	0	12	24	36	48	60	72	84	96	106	120	132	144	156	168	180
2x/weekly	85	84	75	64	58	50	47	43	39	31	21	13	10	6	2	0
3x/weekly	70	66	50	41	34	26	8	2	0							

Fig. 2 Biochemical relapse-free survival rates for patients treated twice weekly vs. thrice weekly

1990; Lai et al. 1990, 1991). More recently, other studies explored the same issue and failed to observe any influence of OTT on biochemical control (Horwitz et al. 1997; Dong et al. 2018). Indeed, in a cohort of 470 patients similar results were observed by Horwitz et al., for patients treated either in ≤ 7, 8–9, or ≥ 9 weeks (Horwitz et al. 1997). Recently, Dong et al., reported on 1728 men treated with dose escalation (≥ 74 Gy in 1.8 or 2 Gy per fraction) (Dong et al. 2018). In their series, unintentional treatment breaks were not associated with outcome independently from risk groups.

The negative results of the above quoted studies are questioned by others suggesting a detrimental impact of OTT. In a larger single institution study on 1796 men treated with EBRT with 76 Gy (median dose), D'Ambrosio et al., created the concept of "non-treatment day ratio" (NTDR) (i.e., number of non-treatment days divided by the total elapsed days of EBRT) and observed that a NTDR ≥ 33% was a significant predictor for bRFS but only for low-risk patients (D'Ambrosio et al. 2008). Similar results were confirmed in a multicenter cohort of 4839 men treated between 1987 and 1995 for which OTT impacted negatively long-term bRFS in low- and intermediate-risk patients treated with doses of 70 Gy or higher (Thames et al. 2010).

An artefactual increase of the α/β value of prostate cancer cells from 1.4 Gy to > 2.7 Gy (95% CI 1.6–3.8) has been estimated due to an OTT longer than the 4–5-week lag-time secondary to an accelerated repopulation of clonogenic cells (Miralbell et al. 2012; Vogelius and Bentzen 2018). This might translate in our series in a decrease of the biologically effective dose from 91 to 87.4 Gy and 82.5 Gy for the thrice-weekly and twice-weekly treatment schedules, respectively (Vogelius and Bentzen 2018). Despite the potential outcome impact of this 5-Gy difference between the two schedules, the similarity of bRFS results at 5 years in our series may be probably explained by a dose–response saturation effect observed with ≥ 80 Gy effective dose (Vogelius and Bentzen 2018), even if a longer follow-up is probably needed to confirm these results.

The potential negative impact of long OTT on repopulation may be balanced by the delivery of higher EBRT doses (Perez et al. 2004). Indeed, the addition of a single 4 Gy fraction to the 14 × 4 Gy (i.e., 60 Gy total dose) in a twice-weekly schedule improved 5-year bRFS compared to patients treated to 56 Gy also twice weekly (Kountouri et al. 2016). However, the 60 Gy total dose, turned to be equivalent to 87.6 Gy (OTT-corrected $NTD_{2\,Gy}$), very similar than

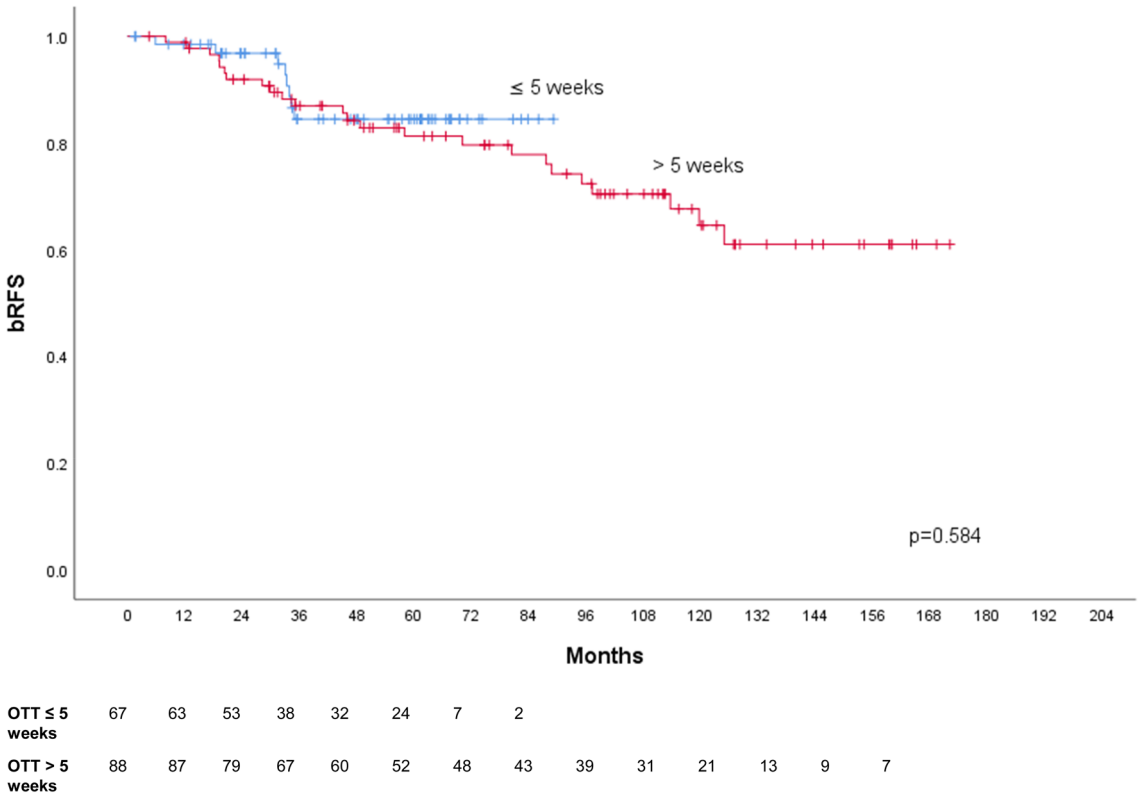


Fig. 3 Biochemical relapse-free survival rates for patients treated with an OTT ≤ 5 weeks vs. an OTT > 5 weeks

the 87.4 Gy (OTT-corrected $NTD_{2\ Gy}$) for patients treated to 56 Gy thrice weekly.

Radiation-induced toxicity and OTT have been mostly explored in extreme hypofractionated schedules. Delivering 37.25 Gy in five fractions, King et al., observed a significantly higher rate of rectal toxicity by treating on five consecutive days compared to an every-other-day (EOD) schedule (King et al. 2009). More recently, the PATRIOT trial, a multicenter Canadian phase II study, investigated the impact of OTT on quality of life in low- and intermediate-risk prostate cancer patients treated with 40 Gy in five fractions by randomizing patients between EOD and once-a-week schedule (Quon et al. 2018). Patients treated once weekly showed an improved acute bowel and urinary quality of life outcome compared to men treated EOD with the same dose (Quon et al. 2018).

Although, no differences were observed at the end of the EBRT between patients treated two or three times weekly in our study, a higher rate of persistent grade-2 GU toxicity was observed at 6 weeks and later on in patients treated with the more accelerated regimen. These findings are supported by results of a UK phase I/II dose-escalation IMRT study treating the whole pelvis and prostate with conventional 2 Gy fractions or moderate hypofractionation (60 Gy to the prostate with 47 Gy to the pelvic lymph nodes with daily fractions of 3 Gy and 2.35 Gy) delivered four or five times per week (Reis Ferreira et al. 2017). Acute GU and GI toxicities as well as late GI side effects were significantly reduced by extending the OTT over 4–5 weeks. Furthermore, GU and GI acute grade-2 toxicities were slightly higher in the accelerated arm of a randomized phase III hypofractionated Belgian trial comparing 56 Gy in 16 fractions of 3.5 Gy over 4 weeks to 67 Gy in 25 fractions of 2.68 Gy over 5 weeks (Fonteyne et al. 2018).

Looking at differences in repositioning techniques among the two cohorts, no impact of image guidance on urinary toxicity was observed in our study between patients treated in less vs. more than 5-week OTT. Considering that patients experiencing the higher GU side effects were those treated with IGRT techniques, it may be speculated that the time factor may outweigh the impact of repositioning techniques on GU toxicity occurrence after moderate hypofractionation.

Limitations of this study stem first in its retrospectivity analyzing a small cohort of patients over a 14-year period. Moreover, marked differences of median follow-up intervals between both groups of patients introduce additional bias especially in the evaluation of long-term disease control, although the occurrence of the grade-2 toxicities in the thrice-weekly group was mostly observed during the first 3 years following the irradiation. Furthermore, inherent

heterogeneities in tumor characteristics (i.e., a significantly higher number of patients with a GS 7 in the thrice-a-week treatment group), differences in treatment techniques (i.e., possibly more accurate, for patients treated thrice-a-week), and no prospective quality of life and patient-reported outcome evaluation should all be considered additional pitfalls potentially weakening the reliability of the results presented in this report.

Conclusions

Less vs. more than 5 weeks OTT may increase acute and late GU side effects without significantly improving bRFS in patients treated with high effective doses ($\geq$ 82 Gy) with moderate hypofractionated RT for prostate cancer. Nevertheless, the role of OTT on long-term outcome and toxicity of prostate cancer patients treated with hypofractionation deserves further prospective evaluation. Based on radiobiological modeling and the differential α/β ratio for prostate cancer cells in the presence of a time factor, efforts to find an optimal balance between OTT reduction and toxicity profile should be attempted when delivering moderate hypofractionation schedules.

Acknowledgements This study has been funded by a research grant from the "Fundació Privada Cellex", Spain and the "Fondation pour la lutte contre le cancer et pour des recherches médico-biologiques", Geneva, Switzerland.

Author contributions All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

Amdur RJ, Parsons JT, Fitzgerald LT, Million RR (1990) The effect of overall treatment time on local control in patients with adenocarcinoma of the prostate treated with radiation therapy. Int J Radiat Oncol Biol Phys 19(6):1377–1382

D'Ambrosio DJ, Li T, Horwitz EM, Chen DY, Pollack A, Buyyounouski MK (2008) Does treatment duration affect outcome after radiotherapy for prostate cancer? Int J Radiat Oncol Biol Phys 72(5):1402–1407. https://doi.org/10.1016/j.ijrobp.2008.03.011

Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, Graham J, Kirkbride P, Logue J, Malik Z, Money-Kyrle J, O'Sullivan JM, Panades M, Parker C, Patterson H, Scrase C, Staffurth J, Stockdale A, Tremlett J, Bidmead M, Mayles H, Naismith O, South C, Gao A, Cruickshank C, Hassan S, Pugh J, Griffin C, Hall E, Investigators CH (2016) Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 17(8):1047–1060. https://doi.org/10.1016/S1470-2045(16)30102-4

Diaz A, Roach M IIIrd, Marquez C, Coleman L, Pickett B, Wolfe JS, Carroll P, Narayan P (1994) Indications for and the significance of seminal vesicle irradiation during 3D conformal radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 30(2):323–329

Dong Y, Zaorsky NG, Li T, Churilla TM, Viterbo R, Sobczak ML, Smaldone MC, Chen DY, Uzzo RG, Hallman MA, Horwitz EM (2018) Effects of interruptions of external beam radiation therapy on outcomes in patients with prostate cancer. J Med Imaging Radiat Oncol 62(1):116–121. https://doi.org/10.1111/1754-9485.12675

Fonteyne V, Sarrazyn C, Swimberghe M, De Meerleer G, Rammant E, Vanderstraeten B, Vanpachtenbeke F, Lumen N, Decaestecker K, Colman R, Villeirs G, Ost P (2018) 4 weeks versus 5 weeks of hypofractionated high-dose radiation therapy as primary therapy for prostate cancer: interim safety analysis of a randomized phase 3 trial. Int J Radiat Oncol Biol Phys 100(4):866–870. https://doi.org/10.1016/j.ijrobp.2017.12.016

Gao M, Mayr NA, Huang Z, Zhang H, Wang JZ (2010) When tumor repopulation starts? The onset time of prostate cancer during radiation therapy. Acta Oncol 49(8):1269–1275. https://doi.org/10.3109/0284186X.2010.509737

Graf R, Wust P, Hildebrandt B, Gogler H, Ullrich R, Herrmann R, Riess H, Felix R (2003) Impact of overall treatment time on local control of anal cancer treated with radiochemotherapy. Oncology 65(1):14–22. https://doi.org/10.1159/000071200

Haustermans KM, Hofland I, Van Poppel H, Oyen R, Van de Voorde W, Begg AC, Fowler JF (1997) Cell kinetic measurements in prostate cancer. Int J Radiat Oncol Biol Phys 37(5):1067–1070

Horwitz EM, Vicini FA, Ziaja EL, Dmuchowski CF, Stromberg JS, Gustafson GS, Martinez AA (1997) An analysis of clinical and treatment related prognostic factors on outcome using biochemical control as an end-point in patients with prostate cancer treated with external beam irradiation. Radiother Oncol J Eur Soc Ther Radiol Oncol 44(3):223–228

Incrocci L, Wortel RC, Alemayehu WG, Aluwini S, Schimmel E, Krol S, van der Toorn PP, Jager H, Heemsbergen W, Heijmen B, Pos F (2016) Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 17(8):1061–1069. https://doi.org/10.1016/S1470-2045(16)30070-5

King CR, Brooks JD, Gill H, Pawlicki T, Cotrutz C, Presti JC Jr (2009) Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. Int J Radiat Oncol Biol Phys 73(4):1043–1048. https://doi.org/10.1016/j.ijrobp.2008.05.059

Koukourakis M, Hlouverakis G, Kosma L, Skarlatos J, Damilakis J, Giatromanolaki A, Yannakakis D (1996) The impact of overall treatment time on the results of radiotherapy for nonsmall cell lung carcinoma. Int J Radiat Oncol Biol Phys 34(2):315–322

Kountouri M, Zilli T, Rouzaud M, Dubouloz A, Linero D, Escude L, Jorcano S, Miralbell R (2016) Moderate hypofractionated protracted radiation therapy and dose escalation for prostate cancer: do dose and overall treatment time matter? Int J Radiat Oncol Biol Phys 94(2):272–279. https://doi.org/10.1016/j.ijrobp.2015.10.055

Lai PP, Perez CA, Shapiro SJ, Lockett MA (1990) Carcinoma of the prostate stage B and C: lack of influence of duration of radiotherapy on tumor control and treatment morbidity. Int J Radiat Oncol Biol Phys 19(3):561–568

Lai PP, Pilepich MV, Krall JM, Asbell SO, Hanks GE, Perez CA, Rubin P, Sause WT, Cox JD (1991) The effect of overall treatment time on the outcome of definitive radiotherapy for localized prostate

carcinoma: the Radiation Therapy Oncology Group 75-06 and 77-06 experience. Int J Radiat Oncol Biol Phys 21(4):925–933

Lee WR, Dignam JJ, Amin MB, Bruner DW, Low D, Swanson GP, Shah AB, D'Souza DP, Michalski JM, Dayes IS, Seaward SA, Hall WA, Nguyen PL, Pisansky TM, Faria SL, Chen Y, Koontz BF, Paulus R, Sandler HM (2016) Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. J Clin Oncol 34(20):2325–2332. https://doi.org/10.1200/JCO.2016.67.0448

Leyh-Bannurah SR, Karakiewicz PI, Pompe RS, Preisser F, Zaffuto E, Dell'Oglio P, Briganti A, Nafez O, Fisch M, Steuber T, Graefen M, Budaus L (2018) Inverse stage migration patterns in North American patients undergoing local prostate cancer treatment: a contemporary population-based update in light of the 2012 USPSTF recommendations. World J Urol. https://doi.org/10.1007/s00345-018-2396-2

Miralbell R, Roberts SA, Zubizarreta E, Hendry JH (2012) Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: alpha/beta = 1.4 (0.9–2.2) Gy. Int J Radiat Oncol Biol Phys 82(1):e17–e24. https://doi.org/10.1016/j.ijrobp.2010.10.075

Murphy CT, Galloway TJ, Handorf EA, Egleston BL, Wang LS, Mehra R, Flieder DB, Ridge JA (2016) Survival impact of increasing time to treatment initiation for patients with head and neck cancer in the United States. J Clin Oncol 34(2):169–178. https://doi.org/10.1200/JCO.2015.61.5906

Perez CA, Grigsby PW, Castro-Vita H, Lockett MA (1995) Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. Int J Radiat Oncol Biol Phys 32(5):1275–1288. https://doi.org/10.1016/0360-3016(95)00220-S

Perez CA, Michalski J, Mansur D, Lockett MA (2004) Impact of elapsed treatment time on outcome of external-beam radiation therapy for localized carcinoma of the prostate. Cancer J 10(6):349–356

Quon HC, Ong A, Cheung P, Chu W, Chung HT, Vesprini D, Chowdhury A, Panjwani D, Pang G, Korol R, Davidson M, Ravi A, McCurdy B, Zhang L, Mamedov A, Deabreu A, Loblaw A (2018) Once-weekly versus every-other-day stereotactic body radiotherapy in patients with prostate cancer (PATRIOT): a phase 2 randomized trial. Radiother Oncol J Eur Soc Ther Radiol Oncol 127(2):206–212. https://doi.org/10.1016/j.radonc.2018.02.029

Reis Ferreira M, Khan A, Thomas K, Truelove L, McNair H, Gao A, Parker CC, Huddart R, Bidmead M, Eeles R, Khoo V, van As NJ, Hansen VN, Dearnaley DP (2017) Phase 1/2 dose-escalation study of the use of intensity modulated radiation therapy to treat the prostate and pelvic nodes in patients with prostate cancer. Int J Radiat Oncol Biol Phys 99(5):1234–1242. https://doi.org/10.1016/j.ijrobp.2017.07.041

Roach M IIIrd, Marquez C, Yuo HS, Narayan P, Coleman L, Nseyo UO, Navvab Z, Carroll PR (1994) Predicting the risk of lymph node involvement using the pre-treatment prostate specific antigen and Gleason score in men with clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 28(1):33–37

Roach M IIIrd, Hanks G, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH, Sandler H (2006) Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 65(4):965–974. https://doi.org/10.1016/j.ijrobp.2006.04.029

Thames HD, Kuban D, Levy LB, Horwitz EM, Kupelian P, Martinez A, Michalski J, Pisansky T, Sandler H, Shipley W, Zelefsky M, Zietman A (2010) The role of overall treatment time in the outcome of radiotherapy of prostate cancer: an analysis of biochemical failure in 4839 men treated between 1987 and 1995. Radiother Oncol J Eur Soc Ther Radiol Oncol 96(1):6–12. https://doi.org/10.1016/j.radonc.2010.03.020

Vogelius IR, Bentzen SM (2018) Dose response and fractionation sensitivity of prostate cancer after external beam radiation therapy: a meta-analysis of randomized trials. Int J Radiat Oncol Biol Phys 100(4):858–865. https://doi.org/10.1016/j.ijrobp.2017.12.011

Withers HR, Taylor JM, Maciejewski B (1988) The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 27(2):131–146

Zilli T, Jorcano S, Rouzaud M, Dipasquale G, Nouet P, Toscas JI, Casanova N, Wang H, Escude L, Molla M, Linero D, Weber DC, Miralbell R (2011) Twice-weekly hypofractionated intensity-modulated radiotherapy for localized prostate cancer with low-risk nodal involvement: toxicity and outcome from a dose escalation pilot study. Int J Radiat Oncol Biol Phys 81(2):382–389. https://doi.org/10.1016/j.ijrobp.2010.05.057

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.