Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Treatment outcomes with hypofractionated high-dose radiation therapy for prostate cancer

*Gustavo Arruda Viani**, *Bruno Tiago Rossi*, *Elton Suguikawa*, *Gisele Zuliani*, *Eduardo Jose Stefano*

Department of Radiation Oncology, Marilia Medical School, Marília, São Paulo, Brazil

ARTICLE INFO

Article history:
Received 26 February 2015
Received in revised form
26 May 2015
Accepted 1 December 2015
Available online 12 February 2016

Keywords:
3D-CRT
Late toxicity
Biochemical control
Outcomes

ABSTRACT

Aim: To report the treatment results of a retrospective cohort of prostate cancer patients treated with Hypo-RT with a high equivalent biological effective dose (BED).

Background: Hypofractionated radiotherapy (Hypo-RT) has gained popularity and interest in the treatment of prostate cancer. However, there are few experiences with adequate follow-up reporting treatment results using high equivalent dose with Hypo-RT.

Materials and methods: We assigned 149 men with low-, intermediate- and high-risk prostate cancer to receive Hypo-RT with a total dose of 69 Gy/23 fractions. Late gastrointestinal (GI) and genitourinary (GU) toxicity were prospectively evaluated according to modified RTOG criteria. Biochemical no evidence of disease (bNED) was defined as the nadir prostate-specific antigen level plus 2 ng/mL.

Results: The median follow-up was 53 months. For the entire cohort, the 5-year bNED rate was 94.6%, and for low-, intermediate- and high-risk patients the 5-year bNED was 100%, 96.4%, and 86% ($p = 0.007$), respectively. The 5-year overall survival rate was 92%. Only 1 patient died from the disease at 48 months after treatment, giving a 5-year cancer-specific survival of 98%. The worst grade ≥2 rate GI and GU toxicity was 13.4% and 14%, respectively. No grade >3 toxicity was observed. The presence of grade ≥2 GI and GU toxicity at the last follow-up was only 1.3% and 3%, respectively.

Conclusions: Hypo-RT (69 Gy/23 fractions) with a high equivalent BED produces excellent rates of biochemical control for low, intermediate and high-risk prostate cancer. The long term GU and GI toxicity rates were considered low and acceptable.

* *Corresponding author at*: Department of Radiation Oncology, Marilia Medical School, Maria Cecilia Alves, 192, Marilia, São Paulo, Brazil. Tel.: +55 14 3454 2065; fax: +55 14 3432 1780.
E-mail address: gusviani@gmail.com (G.A. Viani).

http://dx.doi.org/10.1016/j.rpor.2015.12.003

1. Background

In the last decades, randomized clinical trials and meta-analyse have showed that higher radiotherapy doses (>74 Gy) produce better biochemical control than conventional doses (<74 Gy).[1–3] Evidence from experimental and clinical studies suggest that prostate cancer has a lower α/β ratio than the surrounding organs.[4,5] This relationship between the α/β has raised the idea that a hypofractionated schedule might be more advantageous in terms of patient convenience, cost, and resource utilization than conventional schedules.[6] The clinical results of randomized clinical trials have also supported the practice of hypofractionated schedule in patients with localized prostate cancer.[7–10] These studies show that the hypofractionated schedule with high biological effective dose produces similar biochemical control and toxicity rates to conventional fractionation. However, there are a few clinical reports with adequate follow-up describing the clinical results with the use of hypofractionated high-dose radiotherapy (HypoHD-RT). In 2009, we decided to introduce this hypofractionated schedule in our clinical practice. The decision was made based on the clinical results of dose escalation trials and due to the concept of the low α/β ratio of prostate cancer. In 2013, we compared this hypofractionated schedule with the conventional one (78 Gy in 39 fractions) in terms of acute toxicity.[16]

2. Aim

In this report, we analyzed the treatment outcomes in terms of late gastro-intestinal (GI) and genitourinary (GU) toxicity, and biochemical control of a cohort of 149 men with prostate cancer who receive HypoHD-RT.

3. Materials and methods

The present study is a retrospective cohort with data prospectively collected in a single institution. The study enrolled 149 prostate cancers with localized disease. The study began in November 2009 and closed in January 2011. The ethic committee of our institution has approved the present work.

4. Evaluation

All patients, before the treatment, were evaluated by a full history and physical examination. Patients were classified into low, intermediate and high-risk group according to their Gleason score, T stage and initial PSA (iPSA). Low-risk group included patients with Gleason score <7/stage T1–T2a, and iPSA <10 ng/mL. Intermediate risk included Gleason score <7, or Stage T1–T2b, or iPSA level of 10–20 ng/mL; and high-risk patients with Gleason score >7, or Stage >T2b, or iPSA >20 ng/mL. All patients classified as high risk were submitted to the bone scans. Patients with metastases, prior history of prostatectomy, pelvic radiotherapy treatment, or chemotherapy treatment were excluded of this study.

5. Treatment

The 3D-CRT plan consisted of six fields to deliver a total dose of 69 Gy/23 fractions of a single daily dose of 3 Gy. The prescribed dose should cover 95% of PTV.

By the linear-quadratic formula, considering an α/β ratio of 1.5 Gy for prostate cancer, 69 Gy/23 fractions are equivalent to 88.7 Gy in fractions of 2 Gy. All patients were simulated on CT simulator. Patients were advised that extreme bladder or rectal filling could not be present at the time of the planning CT. An enema before the planning CT scan to empty the rectum and 2 glasses of water were recommended. A triangle sponge under the knees was used for all patients on the treatment planning CT. The following structures were contoured as organs at risk; femoral heads, rectum, bladder, and penile bulb. The contours of structures followed the recommendations of RTOG.[11] The rectum was contoured from the anal verge to the rectosigmoid transition. The low-risk group had only the prostate gland countered as clinical target volume (CTV). Intermediate and high-risk group had the prostate gland plus the seminal vesicles base (1 cm) contoured as CTV. The planning target volume (PTV) was created with 1 cm margin on the CTV, except for the rectal wall (7 mm). A single-radiation oncologist did all contours, and other two checked it. The study used the following rectal dose volume histogram (DVH); V50 < 50%, V60 < 35%, V65 < 25%, V70 < 20%, and V75 < 15%. To adapt the DVH for a hypofractionated schedule, the equivalent DVH to the dose of 3 Gy by fraction (assuming $\alpha/\beta = 3$ Gy) was calculated. Consequently, the rectal DVH constraints for hypofractionated were V42 Gy $\leq$ 50%, V51 Gy $\leq$ 35%, V58 Gy $\leq$ 25% and V62 Gy $\leq$ 15%. The following adapted bladder DVH constraints were used; V54 Gy $\leq$ 50%, V58 Gy $\leq$ 35%, V62 Gy $\leq$ 25% and V65 Gy $\leq$ 15%. All the treatment planning was performed by the Eclipse version 7.0 (Varian Medical Systems, Inc, Palo Alto, USA). All fields were treated daily in a megavoltage linear accelerator – 6 MV with 120-multileaf collimators. The digital portal images with X-ray using bone landmarks were obtained before the treatment for all patients. Patients with no set-up error on the first digital portal image were checked weekly. Patients with set-up errors on the digital portal images were checked with repeat imaging (three sequential images). Patients without set-up errors on the repeat imaging were checked by orthogonal images weekly. Only set-up errors greater than 2 mm were corrected.

Patients classified as intermediate, and high-risk group underwent an androgen blockage. The androgen blockage was done with acetate of goserelin of 3.6 mg. A total of 6 and 24 months of androgen blockage (neoadjuvant, concomitant and adjuvant) were administered for patients classified as intermediate and high-risk group, respectively.

6. End points

The primary endpoint of this trial was biochemical control defined as nadir+2 ng/mL, according to PHOENIX criteria.[12] Late toxicity was considered as any treatment reaction developed after 3 months of treatment. The radiation oncologists collected toxicity data prospectively. The RTOG system

was used to score the toxicity. The toxicity data were collected weekly during the treatment with documentation of acute toxicity.[13] The evaluation after RT included serum PSA and testosterone determination, and documentation of treatment-related toxicity at 3–6 months for the first 5 years. Trained radiation oncologists performed all toxicity assessments.

7. Statistical analysis

Overall, cancer-specific, progression-free and biochemical relapse-free survival (biochemical no evidence of disease [bNED]) were calculated by the Kaplan–Meier actuarial method.[14] Statistical analyzes were performed using Statistical Analysis Systems software (SPSS). p values < 5% was considered significant.

8. Results

Between 2009 and 2011, 149 patients were treated with our hypofractionated radiotherapy schedule. All patients completed the full treatment, and no patient was lost of the follow-up. According to the D' Amico risk group stratification,[15] 34.2%, 36.9%, and 28.8% of the patients had low-, intermediate- and high-risk prostate cancer, respectively. Table 1 describes the characteristics of all the patients.

9. Overall survival, prostate cancer specific survival and progression-free survival

During the follow-up, 11 patients died from other diseases than prostate cancer and none of them with biochemical failure. Only one patient classified as high-risk disease died of prostate cancer. The 5-year OS rate was 92.6%, as described in Fig. 1a. According to the risk group classification, the 5-year OS rate was 94.1%, 92.2%, and 90.2% ($p = 0.819$), for the low-, intermediate- and high-risk group, respectively. The prostate cancer-specific survival at 5 years was 98%, Fig. 1b. In general, the progression-free survival rate at 5 years was 86.6%, and 94%, 89% and 74% ($p = 0.019$) for the low-, intermediate- and high-risk group, respectively, Fig. 2a.

Table 1 – Baseline characteristics of the 149 patients.

Characteristic	N (%)
Patients (*n*)	149
Age (median)	70 (44–76)
Clinical stage	
T1a	1 (0.6%)
T1b	1 (0.6%)
T1c	90 (60.4%)
T2a	30 (20.1%)
T2b	15 (10%)
T2c	6 (4%)
T3a	6 (4%)
Baseline Gleason score	
2–6	76 (51%)
7	51 (34%)
8–10	22 (15%)
Initial PSA level (ng/mL)	
Mean	18.6
Range	3.2–115
Risk stratification	
Low risk	51 (34.2%)
Intermediate risk	55 (36.9%)
High risk	43 (28.8%)
Androgen treatment	98 (65.7%)
Comorbidities (hypertension or diabetes)	58 (39%)
Follow-up (mo)	53 (24–62)

10. Biochemical control

The median follow-up time of 53 months (range, 24–63 months). The 5-year bNED for the entire cohort was 94.6%. The 5-year bNED for low-, intermediate- and high-risk prostate cancer was 100%, 96.4% and 86%, respectively ($p = 0.007$), Fig. 2b. Among the eight patients with biochemical failure, 5 progressed to bone metastases, all salvaged with early androgen deprivation. No patient in whom biochemical failure was found had a regional nodal relapse. Among the 5 patients with bone metastases, one became hormone refractory receiving chemotherapy and progressed to death at 48 months from the radiotherapy ending.

11. Late toxicity

The maximal (or worst) late toxicity score and the toxicity evaluated at the last follow-up are summed in Table 2. During the follow-up, the evaluation of patients with any degree of rectal bleeding was performed for colonoscopic. Maximal late GI toxicity, classified according to RTOG/EORTC late radiation morbidity, is described in Table 2. All patients with rectal bleeding graduated as grade-2 or higher underwent a 4% formalin enema. Six patients required only 1 blood transfusion due to a low hemoglobin level. The maximal late toxicity for Grade 2 or higher during the entire period of follow-up was 13.4% (Fig. 3). At the last visit, only 2 patients (1.3%) remained with Grade 2. There was no Grade 3, 4 or 5 GI toxicity. The maximal late GU toxicity detected during the follow-up period was Grade 0 in 28%, Grade 1 in 58%, Grade 2 in 12%, and Grade 3 in 2% of the patients. At the last follow-up visit, 15% remained with Grade 1, only 3% remained with Grade 2, and no Grade 3 GU toxicity at the last follow-up was observed.

12. Discussion

Currently, hypofractionated schedules have gained augmented interest in the treatment of prostate cancer. First, due to the good quality evidence supporting the low α/β ratio of prostate cancer and, second, because of the inherent therapeutic benefit of employing larger fractionated doses. In addition to that, other advantages such as saving treatment time and medical resources and patient's convenience have given to the hypofractionated radiotherapy noted popularity.

In this report, we presented the long-term results of 149 patients with low-/intermediate-/high-risk prostate cancer treated with a HypoHD-RT schedule (69 Gy/23 fractions). The biochemical control and toxicity rates observed here

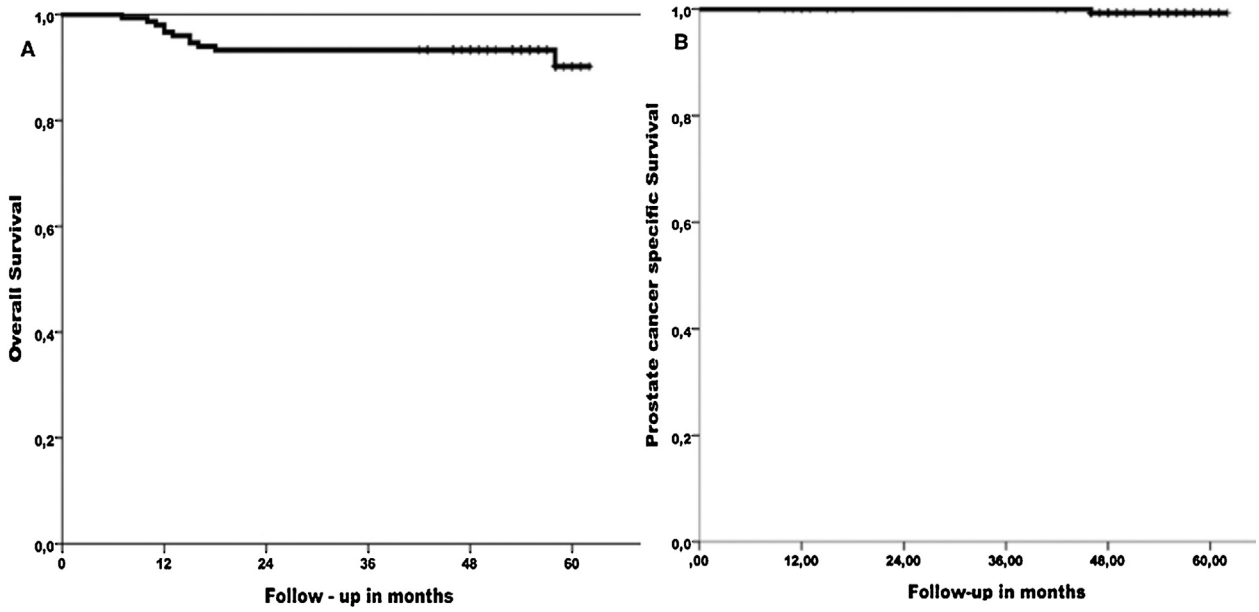

Fig. 1 – (a) Overall survival rate for the entire cohort. (b) Prostate cancer-specific survival for the entire cohort.

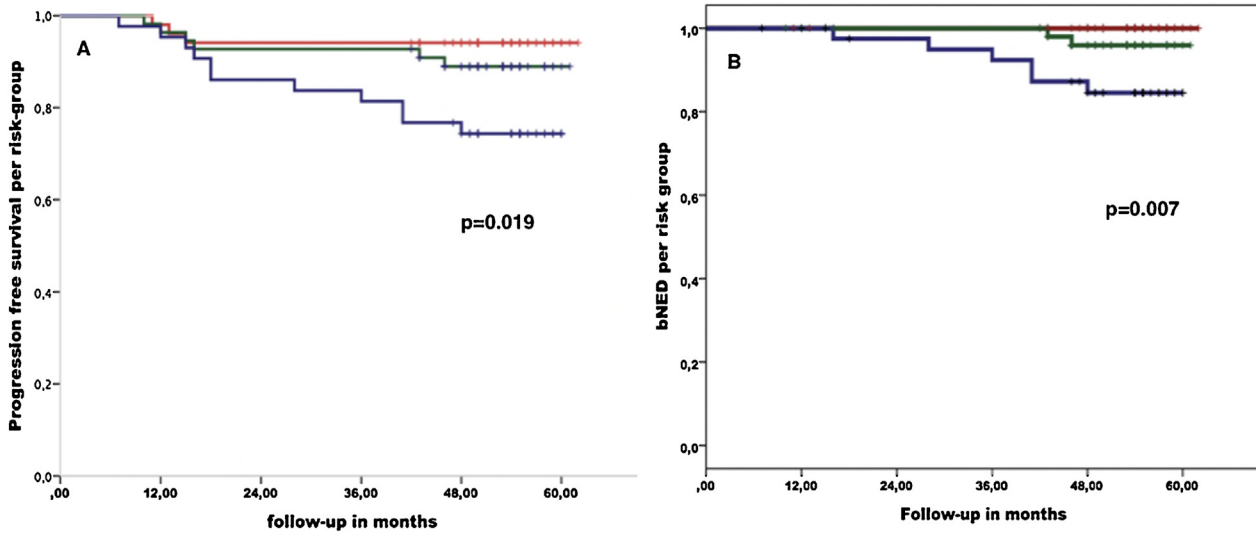

Fig. 2 – (a) Progression-free survival rate stratified according to prostate risk-group. (b) bNED rate stratified according to prostate risk-group. Low – (red), intermediate – (green) and high – risk (blue).

can be considered encouraging, and comparable to the outcomes achieved using other fractionations and radiation techniques. The 5-year bNED for low-/intermediate-risk group (100%/94.6%) of the present study is comparable to the results of Patel et al.[16] In their study, the Canadian group delivered 66 Gy in 22 fractions with 3D-CRT to 129 low-/intermediate-risk prostate cancer patients. With this fractionation, they achieved an actuarial bNED rate 97% at 5 years. The 5-year bNED rate for the high-risk group in the present series (86%) is also comparable to another trial that

Table 2 – Maximal grade of genitourinary and gastrointestinal toxicity documented at any time during the follow-up period, and toxicity grade at the last follow-up.

	Gastrointestinal toxicity			Genitourinary toxicity		
Grade	0	1	≥2	0	1	≥2
Maximal	70.6%	16%	13.4%	28%	58%	14%
At last follow-up	73.7%	25%	1.3%	82%	15%	3%

Table 3 – Studies using Hypo-RT with similar equivalent doses.

Studies	Patients	Dose/fraction	EQ2 for a/b 1.4	Grade 2 ≥late GI/GU toxicity (%)
Arcangeli et al.[9]	168 patients randomized for Hypo-RT or Conv-RT	Arm I: 80 Gy/2 Gy/40 fx ArmII: 62 Gy/3.1 Gy/20 fx	Hypo-RT arm: 82.1	**RTOG** GI: 14% GU: 11%
Patel et al.[16]	129 patients from a retrospective cohort with low risk treated with 3D-CRT and IGRT with daily ultrasound.	3 Gy/22 fx	85.4	**CTC 3.0** GI: 25% GU: 32%
Pollack et al.[7]	307 patients randomized for Hypo-RT or Conv-RT with IMRT	Arm I: 76 Gy/2 Gy/28 fx Arm II: 70.2 Gy/2.7 Gy/26 fx	84.7	**RTOG** GI: 6% GU: 18.5%
Kupelian et al.[18]	770 patients for Hypo-RT with IMRT	70 Gy/2.5 Gy/28 fx	80.2	**RTOG** GI: 4.5% GU: 5.2%
Present study	149 patients from a retrospective cohort of patients treat with 3D-CRT	69 Gy/23 fx	89.2	**RTOG** GI: 13.4% GU: 14%

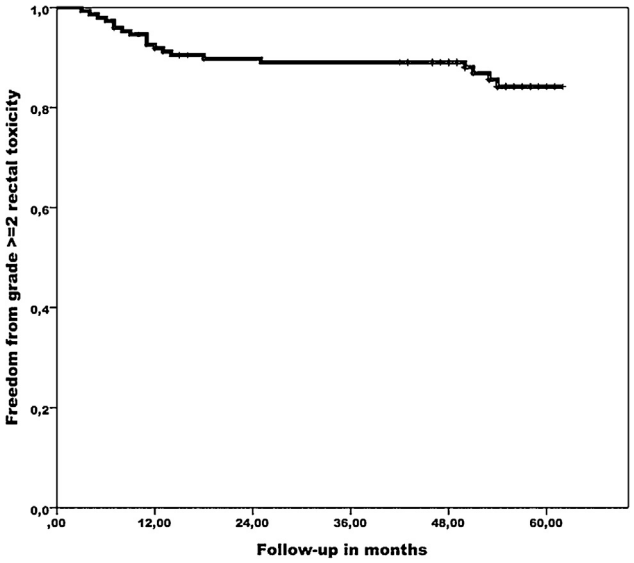

Fig. 3 – Survival freedom of late GI toxicity grade 2 or higher.

used a high equivalent hypofractionated schedule. Arcangeli et al. assigned 168 patients to receive randomly hypo or conventional fractionated schedules with 3D-CRT to the prostate and seminal vesicles combined with total androgen deprivation.[9] The 3-year bNED was 87% for patients from hypofractionated arm.

However, despite the good results recently reported by clinical trials, and the noted popularity, the most frequent doubt to use the hypofractionated high-dose schedule is the concern with severe late toxicity. Our severe rectal toxicity rate, classified as ≥grade 2, shows that the treatment is tolerable and safe. Furthermore, the most of GU and GI toxicity improved over time, making it difficult to graduate it. Due to this difficulty, we used the maximal toxicity and the toxicity at the last follow-up to give a precise idea of changing over the follow-up time. Our rate of late grade ≥2 GI toxicity was 13.4%, with only 1.3% at the last follow-up. Other authors have graduate late toxicity with this approach. For instance, Patel et al.[16] observed a rate of 27% and 32% for late grade ≥2 GI and GU toxicity, respectively, using 3D-CRT with 66 Gy/22 fractions (Table 3). In this Canadian series, Patel and colleagues did not use predefined constraints. Consequently, we speculate that the differences between our study and Patel et al. in terms of late grade ≥2 GI toxicity rate could be related to the use of the predefined rigid constraints. The problem with this speculation is the absence of a consensus on the optimal dosimetric parameters, and also due to the variation of position and volume of the organs at risk during and between the radiotherapy treatment. However, even with these caveats, the present data reinforce the idea that it is better to use a restrictive constraint than not, and it can be a helpful parameter to reduce toxicity.[17]

Thus, although some readers could argue that radiotherapy technique used in the present study is overpassed in some developed countries, this HypoHD-RT schema with 3D-CRT could be the extreme utility to treat prostate cancer in low-income countries. Additionally, it is possible to think or suppose that these results tend to improve with the use of IMRT and IGRT. The preliminary results of CHHIP trial (Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer) support this speculation. In this trial, patients were treated with conventional (74 Gy/2 Gy) or hypofractionated (60 Gy/3 Gy or 57 Gy/3 Gy) IMRT combined with the androgen suppression. With a median follow-up of 50.5 months, there was no significant difference in regard to bowel or bladder toxicity ≥grade 2. The 60 Gy/3 Gy arm had 3.2% and 2.2% of late grade ≥2 GI and GU toxicity.[8] Pollack et al. using 70.2 Gy/26 fractions with intensity modulate radiotherapy (IMRT) and guided image (IGRT) with 4 mm of posterior margin obtained 6% of late grade ≥2 GI toxicity.[7]

Consequently, based on the results of this series and the experience accumulated from other countries with IMRT, currently, we have incorporated the IMRT with rigid constraints to treat prostate cancer patients with Hypo-RT.

13. Conclusion

The present series is the first to show the results of a high-dose Hypo-RT using 3D-CRT with a long-term follow-up. There is little experience reporting regimens delivering high-BED to levels such as 88 Gy in conventionally fractionated RT. Our data show that a HypoHD-RT using 3D-CRT produce an excellent biochemical control and a low rate of late GI and GU toxicity. The prostate risk-group classification had an impact on the rates of biochemical control, reaffirming the need for more dose in patients with high-risk prostate cancer. However, it is important to stress the use of rigid constraints and adequate margins in the absence of IGRT or IMRT to guarantee acceptable rates of late toxicity.

Financial disclosure

None declared.

Conflicts of interest

The author and co-authors have no conflicts of interest to declare.

REFERENCES

1. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* 2009;**74**:1405–18.
2. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the m. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;**70**:67–74.
3. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. *J Clin Oncol* 2010;**28**:1106–11.
4. Miralbell R, Roberts SA, Zubizarreta E, et al. 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* 2012;**82**:e17–24.
5. Leborgne F, Fowler J, Leborgne JH, et al. Later outcomes and alpha/beta estimate from hypofractionated conformal three-dimensional radiotherapy versus standard fractionation for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;**82**:1200–7.
6. Sethukavalan P, Cheung P, Tang CI, et al. Patient costs associated with external beam radiotherapy treatment for localized prostate cancer: the benefits of hypofractionated over conventionally fractionated radiotherapy. *Can J Urol* 2012;**19**:6165–9.
7. Pollack A, Walker G, Horwitz EM, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. *J Clin Oncol* 2013;**31**:3860–8.
8. Dearnaley D, Syndikus I, Sumo G, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the chip randomised controlled trial. *Lancet Oncol* 2012;**13**:43–54.
9. Arcangeli S, Strigari L, Gomellini S, et al. Updated results and patterns of failure in a randomized hypofractionation trial for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;**84**:1172–8.
10. Behrendt K, Nowicka E, Gawkowska-Suwińska M, et al. Early closure of phase II prospective study on acute and late tolerance of hypofractionated radiotherapy in low-risk prostate cancer patients. *Rep Pract Oncol Radiother* 2014;**19**(5):337–42.
11. Gay HA, Barthold HJ, O'Meara E, et al. Pelvic normal tissue contouring guidelines for radiation therapy: a radiation therapy oncology group consensus panel atlas. *Int J Radiat Oncol Biol Phys* 2012;**83**:e353–62.
12. Roach 3rd M, Hanks G, Thames Jr H, et al. 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* 2006;**65**:965–74.
13. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the european organization for research and treatment of cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;**31**:1341–6.
14. Dinse GE, Lagakos SW. Nonparametric estimation of lifetime and disease onset distributions from incomplete observations. *Biometrics* 1982;**38**:921–32.
15. D'Amico AV, Whittington R, Malkowicz SB, et al. Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. *J Clin Oncol* 1999;**17**:168–72.
16. Patel N, Faria S, Cury F, et al. Hypofractionated radiation therapy (66 Gy in 22 fractions at 3 Gy per fraction) for favorable-risk prostate cancer: long-term outcomes. *Int J Radiat Oncol Biol Phys* 2013;**86**:534–9.
17. Vargas C, Martinez A, Kestin LL, et al. Dose-volume analysis of predictors for chronic rectal toxicity after treatment of prostate cancer with adaptive image-guided radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;**62**:1297–308.
18. Kupelian PA, Willoughby TR, Reddy CA, et al. Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland clinic experience. *Int J Radiat Oncol Biol Phys* 2007;**68**:1424–30.