

Prostate Cancer

PSA Bouncing after Short Term Androgen Deprivation and 3D-Conformal Radiotherapy for Localized Prostate Adenocarcinoma and the Relationship with the Kinetics of TestosteroneFadil Akyol^a, Gokhan Ozyigit^{a,*}, Ugur Selek^a, Erdem Karabulut^b^aFaculty of Medicine, Department of Radiation Oncology, Hacettepe University, Ankara, Turkey^bFaculty of Medicine, Department of Biostatistics, Hacettepe University, Ankara, Turkey

Accepted 6 April 2005

Available online 18 April 2005

Abstract

Objectives: To assess the factors effecting PSA bounce and to identify any possible relationship with biochemical control after 3-D conformal radiotherapy (3D-CRT) and total androgen deprivation (TAD) for prostate cancer by evaluating four previously described PSA bounce definitions.

Methods: Between January 1998 and January 2001, 83 consecutive patients with clinically localized prostate cancer were treated by 3D-CRT with neoadjuvant 3 months and/or 6 months adjuvant TAD. All patients had a pretreatment PSA level, at least eight post-external beam radiotherapy (EBRT) PSA and testosterone levels and minimum two years of follow-up. Total radiotherapy dose was 73.6 Gy at ICRU reference point. Four previous definitions of PSA bounce were used: Critz definition (≥ 0.1 ng/mL), Cavanagh definition (≥ 0.2 ng/mL), Hanlon definition (≥ 0.4 ng/mL) and Rosser definition (≥ 0.5 ng/mL) according to original methodology performed to report PSA bounce. Biochemical failure was defined in accordance with the ASTRO consensus guidelines.

Results: The median follow-up time was 40 months. PSA bounce was recorded as follows: Critz definition, 33 patients (40%); Cavanagh definition, 21 patients (25%); Hanlon definition, 11 patients (13%); and Rosser definition, 7 patients (8%). In multivariate analysis, pre-EBRT PSA level and the duration of TAD for Critz definition; age, pre-EBRT PSA and the duration of TAD for Cavanagh definition; age and duration of TAD for Hanlon definition; age and pre-biopsy PSA for Rosser definition were significant independent prognostic factors determining PSA bounce. A significant increase of mean testosterone level in bouncers was detected at the 6th–9th and 18th–21st months. PSA bounce did not predict for PSA failure in multivariate analysis.

Conclusions: We observed no correlation between biochemical failure and PSA bounce. The longer duration of TAD and older age were found to be inversely proportional with PSA bouncing in this cohort. Notably, recovery of testosterone might cause PSA bouncing.

© 2005 Elsevier B.V. All rights reserved.

Keywords: Prostate cancer; Radiotherapy; Androgen deprivation; PSA bounce

1. Introduction

PSA levels are expected to decrease after external beam radiation therapy (EBRT) to nadir, but usually remain detectable. The issue of an appropriate

definition of prostate specific antigen (PSA) failure (biochemical failure) after EBRT has been determined with ASTRO consensus of three consecutive increases [1]; however a single rise in post-EBRT PSA level continues to be a source of considerable anxiety due to the intriguing uncertainty of relationship between PSA bouncing and disease relapse.

* Corresponding author. Tel. +90 312 305 2900; Fax: +90 312 309 2914.
E-mail address: gozyigit@hacettepe.edu.tr (G. Ozyigit).

Various definitions of PSA bounce have been used in the literature. Critz et al. [2] used a PSA bounce as a rise of ≥ 0.1 ng/mL after BRT and EBRT. Cavanagh et al. [3] defined an increase of ≥ 0.2 ng/mL after BRT. Hanlon et al. [4] described a PSA bounce after EBRT as a rise of ≥ 0.4 ng/mL, while Rosser et al. [5] recently used an increase of ≥ 0.5 ng/mL as PSA bounce definition. A PSA bounce phenomenon was not previously reported after 3-dimensional conformal radiotherapy (3D-CRT) and total androgen deprivation (TAD). The aim of this study was to evaluate the frequency of bouncing, the possible factors effecting PSA bounce and to identify any correlation between bouncing and biochemical control (bNED) following 3D-CRT combined with short-term AD (STAD) for prostate cancer by evaluating four previously described PSA bounce definitions.

2. Materials and methods

2.1. Patient characteristics

We analyzed 83 patients with clinical stage T2-T3 prostate adenocarcinoma without radiological evidence of lymph node metastasis and distant spread, who were treated between January 1998 and January 2002 in our institutional protocol. The latter date was chosen to have at least 24 months of follow up. The median age was 68 years (range, 53–79). Patients were staged according to the American Joint Committee for Cancer Staging System (AJCC) 1997 [6]. T stages and Gleason scores of patients are shown in Table 1.

2.2. 3-D Conformal radiotherapy

Clinical target volume (CTV) was prostate and seminal vesicles. Seven 6 MV photon beams (anterior, right and left lateral, right and left anterior oblique, right and left posterior oblique) which were equally weighted were used. A total dose of 70 Gy with daily fraction dose of 2 Gy was prescribed to planning target volume (PTV) in all patients regardless of risk group. ICRU reference point (isocenter) dose was 73.6 Gy.

Table 1

T stage and Gleason scores of patients

	N	%
AJCC Stage		
T2a	31	36
T2b	22	27
T3a	22	27
T3b	8	10
Gleason Score		
2–6	44	65
7	17	21
8–10	12	14

Abbreviations: N = number of patients, AJCC = American Joint Committee for Cancer.

2.3. Short-term androgen deprivation (STAD)

Extracapsular extension (stage T3a-b), PSA ≥ 10 ng/dl and Gleason Score (GS) 7 and above were considered as high risk criteria and in case of even one positive factor, the patient was considered in the high risk group. If all above factors were negative, patients were treated in the low risk group. All patients were administered neoadjuvant TAD with either triptoreline acetate or goserelin acetate and ciproterone acetate for 3 months and thereafter were given 3D-CRT. Total androgen deprivation has been stopped during EBRT. In high risk patients, same TAD regimen was continued for further 6 months after the completion of EBRT. Thus, seventeen patients were in the low and 66 were in the high risk group in our series.

2.4. Biochemical failure and PSA bounce definition

Biochemical relapse failure was determined according to American Society for Therapeutic Radiology and Oncology (ASTRO) consensus definition that is 3 consecutive increases in post treatment PSA after achieving a nadir [1].

Four previous definitions were used according to their original methodology to report PSA bounce [2–5]. Critz definition: PSA bounce is defined by a PSA increase of 0.1 ng/ml or greater above the level before bounce followed by a subsequent decrease to or below that level with PSA 0.2 ng/ml as the floor. Hanlon definition: A minimal rise of 0.4 ng/ml over a 6 month follow up period, i.e., an increase with a slope ≥ 0.07 , followed by a drop in PSA level of any magnitude. The drop in PSA may be immediate or following subsequent maintenance and/or increase in PSA. Additionally, the time lapse between two PSA levels used for slope calculations was required to be at least 30 days. Rosser definition: An initial PSA increase of at least 0.5 ng/ml, followed by a decrease to pre-bounce baseline serum PSA value no more than 60 months after EBRT. Cavanagh definition: A PSA increase of ≥ 0.2 ng/ml, followed by a drop in PSA level of any magnitude.

We have also analyzed the correlation of the kinetic of testosterone (3 months interval changes) with the occurrence of PSA bouncing as well as the correlation with biochemical failure.

2.5. Follow-up

Patients were seen in every 3 months for the first 2 years, 4 months for the 3rd and 4th year every 6 months thereafter. In each visit, total serum PSA, free PSA, total testosterone levels, and prostate volumes were measured. All patients had a pretreatment PSA level and at least eight post-EBRT PSA levels in order to assess PSA bounce.

2.6. Statistical analysis

Biochemical relapse failure date was calculated according to ASTRO consensus definition [1]. The freedom from biochemical failure (bNED) was calculated from the end of 3D-CRT for low risk group or adjuvant TAD for high risk group. Differences in percentages for categorical variables according to bouncing were evaluated using the χ^2 -test. Mann-Whitney *U* test was used for the comparison of differences between the means of continuous variables. Logistic regression analysis was performed to assess the independent predictive factors for PSA bounce. Kaplan-Meier method was used for survival estimates. The Log Rank test was used to evaluate differences between subgroups. Cox proportional hazards regression model was performed for multivariate prognostic factor analysis of bNED. Statistical significance was assigned to *p* values of 0.05 or less. All statistical analyses were performed by SPSS 12.0 (SPSS Inc., Chicago, IL).

3. Results

The median follow-up time was 40 months (range, 24–88 months); 46 months for the low risk, and 39 months for the high risk groups. PSA failure was detected in 19 out of 83 patients. PSA bounce was recorded as follows: Critz definition, 33 patients (40%); Cavanagh definition, 21 patients (25%); Hanlon definition, 11 patients (13%); and Rosser definition, 7 patients (8%).

Univariate analyses are summarized in Table 2. Patients with a recorded PSA bounce had significantly lower pre-biopsy (according to Critz, Cavanagh and Rosser definitions), and pre-EBRT PSA levels (according to Critz and Cavanagh definitions). Older patients less likely experienced a PSA bounce (according to Cavanagh, Hanlon and Rosser definitions). Furthermore, patients receiving only neoadjuvant TAD had significantly higher incidence of PSA bounce in comparison with neoadjuvant plus adjuvant TAD (according to Critz, Cavanagh, and Hanlon definitions). Logistic regression model for multivariate analysis including age, T stage, Gleason score pre-biopsy

PSA, pre-RT PSA, prostate volume, testosterone level and duration of TAD showed that pre-EBRT PSA level and duration of TAD (Critz definition); age, pre-EBRT PSA and duration of TAD (Cavanagh definition); age and duration of TAD (Hanlon definition); age and pre-biopsy PSA (Rosser definition) were significant independent prognostic factors determining PSA bounce (Table 3).

The relationship between testosterone kinetics and PSA bounce is summarized in Table 4. We have found a significant increase in the mean testosterone level of the bouncers at the 6th–9th months according to Critz, Cavanagh, and Hanlon definitions. Similarly, a significant increase in the mean testosterone level of the bouncers was detected according to Critz and Cavanagh definitions at the 18th–21st months. We have not detected any correlation between biochemical failure and the kinetic of testosterone.

To determine whether a PSA bounce was a predictor of biochemical failure, the effect of bounce on bNED was tested. Among four definitions, only Critz definition was found to have a significant impact on bNED in univariate analysis (74% for bouncers and 43% for

Table 2

Effect of different factors on developing a PSA bounce in univariate analyses

	Bounce presence	Critz definition PSA ≥ 0.1	<i>p</i>	Cavanagh definition PSA ≥ 0.2	<i>p</i>	Hanlon definition PSA ≥ 0.4	<i>p</i>	Rosser definition PSA ≥ 0.5	<i>p</i>
Continuous variables									
Mean age (years)	–	68	0.2	68	0.03	68	0.008	68	0.03
	+	66		64		62		62	
Mean prebiopsy-PSA (ng/mL)	–	22	0.007	22	0.001	21	0.09	21	0.05
	+	16		13		14		10	
Mean preEBRT-PSA (ng/mL)	–	2	0.01	2	0.004	1.8	0.056	1.7	0.1
	+	0.8		0.6		0.7		0.7	
Mean Prostate volume (cc)	–	42	0.07	42	0.1	40	0.5	40	0.6
	+	38		38		47		43	
Mean testosterone level (ng/dl)	–	86	0.6	77	0.4	94	0.3	96	0.3
	+	109		154		96		72	
Categorical variables									
T stage									
T2a-b	–	28*	0.1	37	0.2	46	0.8	48	0.8
	+	25		16		7		5	
T3a-b	–	22		25		26		28	
	+	8		5		4		2	
Gleason score									
2–6	–	31	0.2	37	0.08	45	0.2	49	0.5
	+	23		17		9		5	
7–10	–	19		25		27		27	
	+	10		4		2		2	
Duration of TAD									
3 months	–	5	0.004	7	<0.001	12	0.03	14	0.1
	+	12		10		5		3	
9 months	–	45		55		60		62	
	+	21		11		6		4	

TAD = total androgen deprivation.

* Figures represent the number of patients.

Table 3

Factors significantly associated with PSA bounce in logistic regression analyses

	B	p	Exp(B)	95% CI	
Critz definition (PSA ≥ 0.1)					
Pre-EBRT PSA	-0.52	0.05	0.59	0.36	0.987
Duration of TAD	-1.31	0.04	0.27	0.079	0.914
Cavanagh definition (PSA ≥ 0.2)					
Age	-0.16	0.008	0.85	0.75	0.96
Pre-EBRT PSA	-1	0.04	0.37	0.14	0.95
Duration of TAD	-2.36	0.003	0.09	0.02	0.45
Hanlon definition (PSA ≥ 0.4)					
Age	-0.24	0.004	0.78	0.67	0.92
Duration of TAD	-2.89	0.005	0.057	0.007	0.42
Rosser definition (PSA ≥ 0.5)					
Age	-0.20	0.02	0.82	0.69	0.97
Prebiopsy- PSA	-0.19	0.05	0.82	0.68	0.99

Abbreviations: CI = confidence interval, PSA = prostate specific antigen, TAD = total androgen deprivation.

non-bouncers, $p = 0.04$). However, PSA bounce of Critz definition did not predict for PSA failure in multivariate analysis.

4. Discussion

PSA is expected to decrease slowly to reach nadir levels after a successful radiotherapy [7–9]. ASTRO has defined three consecutive PSA rises as a biochemical failure [1]. However, transient increase in PSA level followed by a decrease to preceding value called as PSA bounce is a significant source of anxiety for both clinicians and patients. There are various definitions of PSA bounce after a variety of radiation techniques with or without AD [2–5]. Thus, we performed a study to evaluate PSA bounce phenomena in our patients with prostate cancer via four previously reported definitions. To the best of our knowledge, this is the first study assessing the PSA bounce phe-

nomena in patients treated with 3D-CRT and STAD, as well as its relationship with the kinetics of testosterone.

The previous series evaluating PSA bounce were not consistent in terms of dose, technique or hormonotherapy [2–5,10–12]. In contrast, our data consisted of patients who were uniformly treated in terms of radiation technique (3D-CRT) and dose (73.4 Gy at ICRU point). As all patients were administered STAD, only the duration of AD differed; 3 months for low risk and 9 months for high risk groups.

It can be argued that if the radiobiology of EBRT can be directly compared to that of brachytherapy; this hint is indeed pressing when one compares their PSA bouncing curves. But our methodology of comparing EBRT with BRT is not the first in literature. Similar method was used by others [12]. Stock et al. implied that PSA bounce after brachytherapy may be different from the bounce seen after EBRT [12]. Stock et al. also stated that PSA bounce after EBRT may represent an early manifestation of PSA failure in a certain percentage of patients and the phenomena seen after brachytherapy may seem to have little effect on PSA failure developing; however our data contrasts with their proposal that we found no association between bNED and PSA bounce regardless of the definition used.

Among four definitions, only Hanlon et al. [4] showed a significant relationship of bouncing to bNED control, with bouncers and non-bouncers having 5-year rates of 52% and 69% respectively. They also showed that statistical significance was demonstrated only for patients presenting with pre-biopsy PSA levels <10 ng/ml after stratifying the bouncers with pretreatment PSA level. In current series, we had only 24 patients with pre-biopsy PSA level of 10 and below and among them there were only 3 patients with PSA relapse. Thus, we could not make further subgroup analysis in order to test this issue due to small sample size. Nevertheless Hanlon et al. concluded that bouncing activity should not be used as a sole measure of

Table 4

The relationship between the kinetics of testosterone and PSA bouncing

	Bounce presence	N	Mean testosterone increase at the 6th–9th months (ng/dL)	p	Mean Testosterone increase at the 18th–21th months (ng/dL)	p
Critz definition (PSA ≥ 0.1)	–	50	2	0.02	32	0.05
	+	33	193		108	
Cavanagh definition (PSA ≥ 0.2)	–	62	3	0.02	30	0.03
	+	21	268		160	
Hanlon definition (PSA ≥ 0.4)	–	72	29	0.03	47	0.06
	+	11	230		167	
Rosser definition (PSA ≥ 0.5)	–	76	26	0.08	56	0.07
	+	7	159		155	

N = number of patients.

disease relapse and more importantly, as an indicator for the institution of salvage therapies since half of their patients with PSA bounce were free of biochemical failure.

Evident data related with PSA bounce phenomena in case of AD and radiotherapy is limited. Patel et al. reported that the use of AD did not affect the incidence of PSA bounce using 0.2 ng/ml as PSA increase cut-off in his series of 295 patients treated with BRT and 6 months neoadjuvant AD (62% of cohort) [10]. Similarly, Sengoz et al. also could not detect any PSA bounce difference among 72 patients with prostate cancer receiving EBR-T+AD (82% of cohort) and EBRT alone [11]. They used AD as adjuvant, and the median duration was 6 months (range 4 to 54 months). TAD has a suppressive effect on follow-up PSA levels as expected. Thus, we allowed at least 24 months of follow up for the recovery of testosterone levels. In our series, 13% of patients with TAD according to Hanlon definition showed PSA bounce compared to 17% of patients with AD in Sengoz series which used the same definition. Interestingly, we found that the duration of TAD was inversely proportional with PSA bounce incidence. This finding can not be truly compared with Patel and Sengoz series, because all of our patients received TAD whereas other two series had comparison of their patients between AD and non-AD groups. However we suggest that prolongation of TAD seems to decrease the incidence of PSA bounce. Longer hormone therapy may prevent bouncing as testosterone often does not rise for several months, sometimes a year or more, following completion of LHRH-agonist therapy due to a marked decrease in the number of Leydig cells as well as peritubular thickening and fibrosis in the testis after longer term use of LHRH agonists [13,14]. Therefore, we ensured at least two years of follow-up in our series to allow sufficient period of time for the recovery of androgen levels and its possible influence on PSA levels.

We have detected a higher bounce frequency in younger men compared to older men according to Cavanagh, Hanlon and Rosser definitions in our data while this is an incidental observation; surprisingly it seems to be supported in at least three studies in Critz, Stock and Patel series [10,12,15]. The effect seen with age was hypothesized to be secondary to increased testosterone levels [12]; however the relationship between the PSA bounce and the kinetics of testosterone have not been investigated in the pertinent literature.

In this study, we have demonstrated a significant correlation with the kinetics of testosterone and PSA bouncing. Interestingly we have detected a significant increase in testosterone levels of bouncers only at the 6th to 9th months and the 18th to 21st months after completion of radiotherapy. This rise in testosterone

might have triggered the PSA bounce. The correlation of testosterone kinetics and PSA bouncing for Hanlon and Rosser definitions was not significant but close to significance, possibly due to the small number of bouncers with increasing threshold for PSA bounce. The previous prospective studies showed that the median time to normalization of testosterone in majority of patients took 6–18 months after withdrawal of androgen deprivation therapy [16–21]. In addition, delay in recovery of testosterone after more prolonged periods of androgen suppression can be anticipated; especially with 3 months depot preparations of luteinizing hormone releasing agonists, like we used [16]. Accordingly in our cohort, the first testosterone increase correlated with PSA bounce signify 9 months after the end of neoadjuvant hormone therapy in low risk patients and the second increase was 12 months after the end of adjuvant hormone therapy in high risk patients.

Scattered radiation dose to the testicles above 1 Gy may also depress Leydig cell function [18,22–26]. This observation was mainly based on data using large pelvic fields, which would have generated larger scattered radiation doses to the testis [23–26]. Additionally, the effects of radiation on testicles and the luteinizing hormone suppression may have an additive or synergistic effect on Leydig cell dysfunction [18,25]. Consequently, recovery of Leydig cells following the radiotherapy itself may cause a PSA bounce, just as recovery after hormonal therapy. It is also likely that recovery of Leydig cells after combined hormone therapy and radiotherapy decreases with age [25]. This may explain the negative association between increasing age and occurrence of PSA bounce. Another explanation could be that elderly men are more often treated for high-risk prostate cancer and, hence, are more likely to receive adjuvant hormonal therapy. Furthermore, a direct effect of radiotherapy on the prostate can also be hypothesized. Miller et al. demonstrated a statistically significant increase in serum testosterone levels in 63 patients who had undergone radical prostatectomy [27]. They suggested that there was the production of substance(s) by the prostate that can affect the feedback mechanisms of gonadotrophin secretion. However whether radiotherapy could have a similar effect is not known. If so, PSA bouncing in patients receiving brachytherapy or EBRT without AD may be due to this mechanism of testosterone increase. There were also other hypothesis regarding sexual activity [10,15], or delayed apoptotic event [10] which we did not evaluate in the current study. An evidence based explanation of all those issues is still lacking, therefore needs to be investigated in further trials.

5. Conclusions

PSA bouncing occurs 8–40% of patients treated with 3D-CRT and STAD depending on the bounce definition. We observed no correlation between bio-

chemical failure and PSA bounce. The longer duration of TAD and older age were found to be inversely proportional with PSA bouncing in this cohort. Notably, recovery of testosterone after EBRT+AD seems to cause PSA bouncing.

References

- [1] Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys* 1997; 37:1035–41.
- [2] Critz FA, Williams WH, Benton JB, Levinson AK, Holladay CT, Holladay DA. Prostate specific antigen bounce after radioactive seed implantation followed by external beam radiation for prostate cancer. *J Urol* 2000;163:1085–9.
- [3] Cavanagh W, Blasko JC, Grimm PD, Sylvester JE. Transient elevation of serum prostate-specific antigen following (125)I/(103)Pd brachytherapy for localized prostate cancer. *Semin Urol Oncol* 2000;18:160–5.
- [4] Hanlon AL, Pinover WH, Horwitz EM, Hanks GE. Patterns and fate of PSA bouncing following 3D-CRT. *Int J Radiat Oncol Biol Phys* 2001;50:845–9.
- [5] Rosser CJ, Kuban DA, Levy LB, Chichakli R, Pollack A, Lee AK, et al. Prostate specific antigen bounce phenomenon after external beam radiation for clinically localized prostate cancer. *J Urol* 2002;168:2001–5.
- [6] Fleming I, Cooper J, Henson D, et al. *AJCC cancer staging manual*. 5th ed. Philadelphia: Lippincott-Raven; 1997. p. 47–52.
- [7] Critz FA, Levinson AK, Williams WH, Holladay DA, Holladay CT. The PSA nadir that indicates potential cure after radiotherapy for prostate cancer. *Urology* 1997;49:322–6.
- [8] Critz FA, Williams WH, Holladay CT, Levinson AK, Benton JB, Holladay DA, et al. Post-treatment PSA < or = 0.2 ng/mL defines disease freedom after radiotherapy for prostate cancer using modern techniques. *Urology* 1999;54:968–71.
- [9] Critz FA. Time to achieve a prostate specific antigen nadir of 0.2 ng/ml after simultaneous irradiation for prostate cancer. *J Urol* 2002;168:2434–8.
- [10] Patel C, Elshaikh MA, Angermeier K, Ulchaker J, Klein EA, Chehade N, et al. PSA bounce predicts early success in patients with permanent iodine-125 prostate implant. *Urology* 2004;63:110–3.
- [11] Sengoz M, Abacioglu U, Cetin I, Turkeri L. PSA bouncing after external beam radiation for prostate cancer with or without hormonal treatment. *Eur Urol* 2003;43:473–7.
- [12] Stock RG, Stone NN, Cesaretti JA. Prostate-specific antigen bounce after prostate seed implantation for localized prostate cancer: descriptions and implications. *Int J Radiat Oncol Biol Phys* 2003;56:448–53.
- [13] Giberti C, Barreca T, Martorana G, Truini M, Franceschini R, Rolandi E, et al. Hormonal pattern and testicular histology in patients with prostatic cancer after long-term treatment with a gonadotropin-releasing hormone agonist analogue. *Eur Urol* 1988;15:125–7.
- [14] Huhtaniemi I, Nikula H, Parvinen M, Rannikko S. Histological and functional changes of the testis tissue during GnRH agonist treatment of prostatic cancer. *Am J Clin Oncol* 1988;11(Suppl 1):S11–5.
- [15] Critz FA, Williams WH, Levinson AK, Benton JB, Schnell FJ, Holladay CT, et al. Prostate specific antigen bounce after simultaneous irradiation for prostate cancer: the relationship to patient age. *J Urol* 2003;170:1864–7.
- [16] Nejat RJ, Rashid HH, Bagiella E, Katz AE, Benson MC. A prospective analysis of time to normalization of serum testosterone after withdrawal of androgen deprivation therapy. *J Urol* 2000;164:1891–4.
- [17] Meinhardt W, Horenblas S. Re: Time to normalization of serum testosterone after 3-month luteinizing hormone-releasing hormone agonist administered in the neoadjuvant setting: implications for dosing schedule and neoadjuvant study consideration. *J Urol* 1999;162:170–1.
- [18] Shahidi M, Norman AR, Gadd J, Huddart RA, Horwich A, Dearnaley DP. Recovery of serum testosterone, LH and FSH levels following neoadjuvant hormone cyoreduction and radical radiotherapy in localized prostate cancer. *Clin Oncol (R Coll Radiol)* 2001;13:291–5.
- [19] Dearnaley DP, Norman AR, Shahidi M. Re: Time to normalization of serum testosterone after 3-month luteinizing hormone-releasing hormone agonist administered in the neoadjuvant setting: implications for dosing schedule and neoadjuvant study consideration. *J Urol* 1999;162:170.
- [20] Oefelein MG. Time to normalization of serum testosterone after 3-month luteinizing hormone-releasing hormone agonist administered in the neoadjuvant setting: implications for dosing schedule and neoadjuvant study consideration. *J Urol* 1998;160:1685–8.
- [21] Padula GD, Zelefsky MJ, Venkatraman ES, Fuks Z, Lee HJ, Natale L, et al. Normalization of serum testosterone levels in patients treated with neoadjuvant hormonal therapy and three-dimensional conformal radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;52:439–43.
- [22] Amies CJ, Mameghan H, Rose A, Fisher RJ. Testicular doses in definitive radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 1995;32:839–46.
- [23] Grigsby PW, Perez CA. The effects of external beam radiotherapy on endocrine function in patients with carcinoma of the prostate. *J Urol* 1986;135:726–7.
- [24] Tomic R, Bergman B, Damber JE, Littbrand B, Lofroth PO. Effects of external radiation therapy for cancer of the prostate on the serum concentrations of testosterone, follicle-stimulating hormone, luteinizing hormone and prolactin. *J Urol* 1983;130:287–9.
- [25] Izard MA. Leydig cell function and radiation: a review of the literature. *Radiother Oncol* 1995;34:1–8.
- [26] Shapiro E, Kinsella TJ, Makuch RW, Fraass BA, Glatstein E, Rosenberg SA, et al. Effects of fractionated irradiation of endocrine aspects of testicular function. *J Clin Oncol* 1985;3:1232–9.
- [27] Miller LR, Partin AW, Chan DW, Bruzek DJ, Dobs AS, Epstein JI, et al. Influence of radical prostatectomy on serum hormone levels. *J Urol* 1998;160:449–53.