Original Article

A prospective study of the effect of testosterone escape on preradiotherapy prostate-specific antigen kinetics in prostate cancer patients undergoing neoadjuvant androgen deprivation therapy

David R.H. Christie[a,b,]*, Natalia Mitina[a,c], Christopher F. Sharpley[b]

[a]Genesiscare, Inland Drive, Tugun, Queensland, Australia; [b]Brain-Behaviour Research Group, University of New England, Armidale, Australia; [c]University of Queensland, St Lucia, Queensland, Australia

Abstract

Introduction: Prostate-specific antigen (PSA) kinetic patterns during neoadjuvant androgen deprivation therapy have been shown to predict unfavorable long-term outcomes.

Objective: To investigate the effect of testosterone escape (TE) on these kinetic patterns, as this had not been previously reported.

Methods: There were 50 consecutive prostate cancer patients who received 6 months of triptorelin prior to definitive radiotherapy (RT). Testosterone and PSA levels were measured at baseline and every 6 weeks. Clinical factors were tested for their ability to predict for TE and unfavorable PSA kinetic patterns. The effects of TE, at both 1.7 and 0.7 nmol/L levels, were analyzed.

Results: TE occurred in at least one reading for 14% and 34% of the patients at the 1.7 and 0.7 nmol/L levels, respectively. No baseline factors predicted TE. The median PSA halving time was 25 days and the median pre-RT PSA level was 0.55 ng/mL. The only factor significantly associated with a higher pre-RT PSA level was a higher baseline PSA level. The only factor that significantly predicted a longer PSA halving time was TE at the 1.7 nmol/L level.

Conclusions: TE and higher baseline PSA levels may adversely affect PSA kinetics and other outcomes for patients undergoing neoadjuvant hormone therapy prior to radiotherapy. Studies investigating the tailoring of neoadjuvant therapy by extending the duration in those patients with a higher baseline PSA level or by the addition of anti-androgens in those demonstrating TE, should be considered.

Keywords: Gonadotropin-releasing hormone; Prostate-specific antigen; Prostatic neoplasm; Radiotherapy; Testosterone

1. Introduction

After the initiation of androgen deprivation therapy (ADT) for prostate cancer, the serum testosterone level may briefly flare but then falls to levels that are similar to, or below, that achieved by castration.[1] Despite ongoing treatment with ADT, temporary rises in the level of testosterone may occur, a phenomenon known as testosterone escape (TE). TE was recently identified as a factor affecting the outcome of ADT for patients with metastatic disease, but the significance of it remains controversial.[2] The incidence of TE is generally low, at less than 5%; however, the methods for identifying and measuring it are yet to be standardized. The probability of detecting it for a patient receiving ADT is likely to depend on the number of testosterone measurements taken, the duration of the ADT and the effectiveness of it. A review of the incidence of TE with the available ADT agents was recently published.[1] The significance of the TE has not been investigated in the setting of neoadjuvant ADT (NADT) prior to radiotherapy, so the implications of it are currently unknown.

Most of the previous studies of the testosterone response to ADT have not been intended primarily for the purpose of identifying TE and have been either retrospective or have involved significant heterogeneity.[3] This includes heterogeneity in the stage of the cancer, in other treatments given in addition to ADT (such as surgery and/or radiotherapy), the variety of ADT agents, combinations with antiandrogens, irregular assessments of prostate-specific antigen (PSA) and testosterone levels, and the use of significantly different assays.[4] Not surprisingly the conclusions about the significance of the TE have varied widely. Some have argued that, because the complete (and intentional) TE that occurs during the off-treatment phase when ADT is used intermittently shows minimal effect on long-term cancer control rates, the effect of TE during active treatment must also be minimal, while others have shown TE to be a significant predictor for biochemical failure among patients with metastatic disease.[3,5] Testosterone levels above threshold values of either 0.7 and 1.7 nmol/L (20 and 50 ng/dL) have been associated with the development of castrate-resistant prostate cancer.[6,7] In the

largest study to address the impact of testosterone levels on the outcome of ADT, minimum, median, and maximum levels over a 1-year period were measured in patients suffering biochemical recurrence after definitive treatment, rather than TE, but it was shown that lower levels were associated with longer durations of response.[5] A recent consensus statement from Canada indicated that, although 1.7 nmol/L was the traditional castrate level based on historical assays, newer assay methods and more recent clinical data suggest that 0.7 nmol/L is a more suitable definition.[8]

After initiating ADT, the serum PSA level also usually declines. The response of the PSA level to NADT prior to definitive radiotherapy (the pre-RT PSA) has been investigated and the decline of the PSA to levels below various pre-RT cut-off levels between 0.1 and 1.0 ng/mL has been identified as a favorable prognostic factor.[9] As the duration of NADT has varied and could influence the pre-RT PSA level regardless of the intensity of the response, the response of the PSA has also been measured in terms of the halving time with varying results.[10,11] In a small proportion of patients receiving ADT in this setting, rises in PSA have been observed. This indicates the onset of castration resistance and carries a poor prognosis.[12]

After the neoadjuvant portion of the treatment is completed, patients may discontinue their ADT while having radiotherapy and may opt to not resume ADT afterwards in the hope of achieving a cure without exposure to ongoing ADT side effects. For patients with higher risk disease, ongoing adjuvant ADT after radiotherapy is indicated for periods up to 3 years.[13] However, the duration of the neoadjuvant portion of their ADT treatment, and the agents used, are generally determined by institutional protocols rather than clinical factors and no clear method for individualizing NADT has been established. Significant attempts to individualize NADT have been investigated, including adjustment in the duration of it and the addition of an anti-androgen.[9,14] A better understanding of the effect of ADT on testosterone and PSA levels could contribute to that individualization. It is possible that early identification of either TE or a slow PSA halving time during NADT could predict a less effective contribution from NADT to control of the cancer, in which case adding other agents such as an anti-androgen or an androgen pathway inhibitor might be beneficial. Alternatively, those patients that achieve low testosterone levels, well below castration level and have not yet reached their PSA nadir at 6 months, should perhaps continue to receive NADT for a longer period before proceeding to radiotherapy.

Insights from studies in patients with metastatic disease have shown that the achievement of a lower PSA nadir and a longer time to nadir were found to have a positive effect on progression-free survival.[15] For these patients, the duration of ADT is not limited to 6 months and the nadir may take up to 12 months to be reached. In these cases, no definitive therapy is possible, so the effect of TE can be expressed in terms of the time to biochemical failure. For a patient with localized disease; however, the longer-term outcome is heavily dependent on the definitive radiotherapy component of the treatment, so the effects of TE might be more difficult to identify.

Our aim was to rigorously control all these factors to obtain more reliable information about the response of testosterone to ADT by including patients with intermediate- to high-risk localized disease only, fully staged using standard methods, treated using one ADT agent only, with frequent and regular blood testing, and using one assay method for testosterone and PSA levels over a standard duration (6 months). We hypothesized

that we could then determine whether the TE has any significant impact on the rate of decline in PSA levels and the pre-RT PSA levels, and may thus have a longer-term prognostic effect.

2. Materials and methods

Ethics approval for this study was provided by the Uniting Care Health Human Research Ethics Committee (Registration number 2013.14.85). The study was initiated at GenesisCare sites on the Gold Coast in Tugun and Southport, Australia. ICON cancer care services at the Gold Coast University Hospital were also invited to enter patients into the study.

The present study included 50 consecutive patients presenting between August 2013 and December 2016 with intermediate- and high-risk localized prostate cancer. Eligible patients were previously untreated, biopsy-proven, intermediate-, or high-risk patients with localized disease confirmed by staging bone and CT scans. Eligible patients were stage T2–4N0M0. A baseline MRI scan was done on all patients and the volume of the prostate was measured using a planimetric calculation. Written informed consent and baseline data were obtained. Patients recruited to the study received 6 months of standard NADT with two 3-monthly depot injections of Diphereline™ (triptorelin embonate, hereafter triptorelin) prior to definitive treatment by radiotherapy. Any unexpected or serious toxicity was recorded.

Serum testosterone levels were measured at baseline and every 6 weeks for 6 months subsequently using a chemiluminescent assay. Thus, there were 5 readings per patient and 250 readings altogether. Of these, 50 were baseline levels and 200 were taken after initiation of NADT. The capacity for the NADT to provide a sustained reduction in testosterone levels was analyzed by calculating the frequency of TE. TE was defined at 2 levels: first, levels above 1.7 nmol/L (50 ng/dL, TE1.7), and secondly, at levels above 0.7 nmol/L (20 ng/dL, TE0.7) occurring within these 200 measurements. The number of patients with any TE1.7 or TE0.7 readings, and the average number of TE1.7 and TE0.7 readings per patient were determined. Baseline factors were tested for association with TE1.7 and TE0.7, including age, prognostic risk category (intermediate- vs. High- risk), tumor grade (Gleason scores between 6 and 10), initial PSA and initial testosterone levels.

PSA levels were measured at the same times as the testosterone levels, also using a chemiluminescent assay. The response of the PSA level to NADT was assessed by calculating the PSA halving time and the pre-RT PSA level. The PSA halving times were measured using the formula described by Foo et al.[11] The 5th (and final) PSA level was considered to be the pre-RT PSA level. The same baseline factors were tested for association with the PSA halving time and the pre-RT PSA level, but also the prostate gland volume and frequency of TE were tested. The prostate gland volume was measured by a planimetric calculation from a baseline MRI scan, which was indicated to be the method that provides the most accurate correlation with postprostatectomy volume measurements in a recent systematic review.[16]

After their ADT, the patients proceeded to definitive radiotherapy. The doses, techniques, and the use of subsequent adjuvant hormonal therapies were at the discretion of the treating radiation oncologist. Longer-term outcome data are not yet available.

2.1. Statistical analysis

The sample size was calculated by GPower 3.1, as guided by the primary endpoint, and indicated that a sample of 48 patients was

Table 1

Baseline data.

Variable	Number/median value	Range
Patients' ages, y	76	58–89
Risk group, n		N/A
Intermediate	17	
High	33	
Gleason score, n		N/A
6	1	
7	22	
8	9	
9	18	
10	0	
Prostate volume, mL	38.6	17.3–93.5
Baseline PSA levels, ng/mL	10.4	1.6–57.0
Baseline testosterone levels, nmol/L	10.3	1.3–54.1

N/A = not applicable.

sufficient to detect a large effect size in ANOVA. The significance of factors associated with TE and pre-RT PSA levels were tested by repeated measures ANOVA and linear regression.

3. Results

The study closed to registration when the sample size was achieved. Patients were entered from both GenesisCare (n = 44) and ICON cancer care (n = 6) centers. There were no serious or unexpected toxicities from the NADT. Baseline data are shown in Table 1. Progressive changes in testosterone and PSA levels are shown in Figures 1 and 2. Figure 1 shows that the largest drop in PSA levels occurred between the first and second reading, but further decreases occurred between that and the final reading. Figure 2 shows that the testosterone level dropped profoundly after the first reading, that TE was uncommon and was evenly spread across the remaining readings.

The response of testosterone and PSA levels to the NADT is summarized in Table 2. Testosterone levels dropped from a median baseline value of 10.3 to 0.5 nmol/L at the first assessment, 6 weeks after treatment began. Thereafter, they generally stayed low at
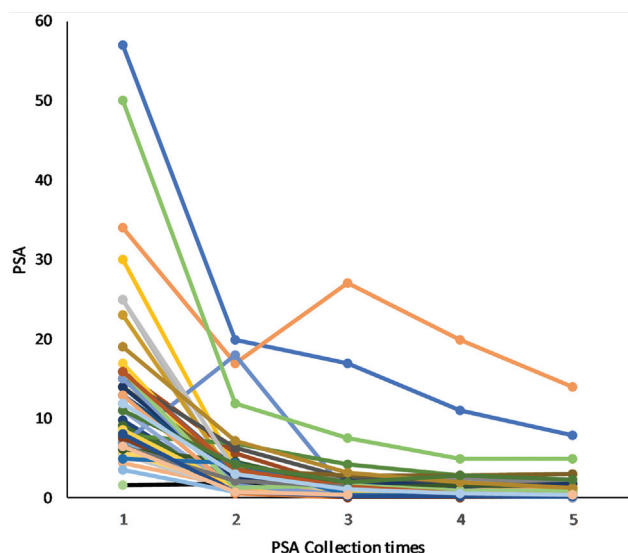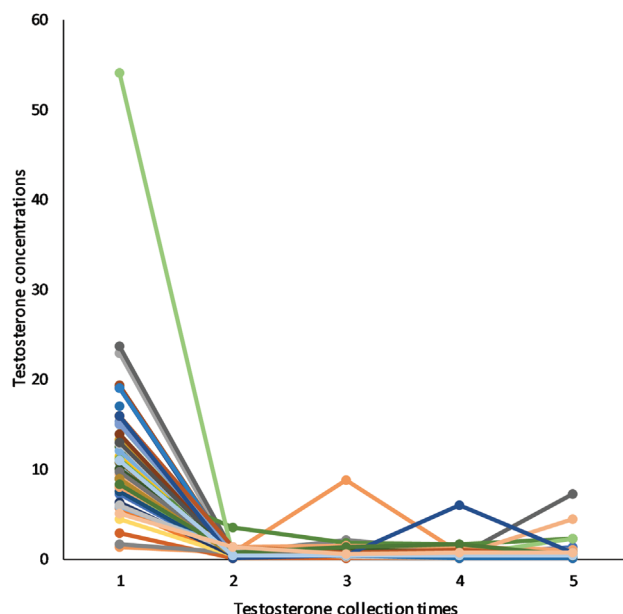

Figure 2. Individual patient testosterone levels (ng/mL).

levels considered below or close to castrate levels. TE1.7 occurred in 9 out of 200 readings, and in 7 of 50 patients. TE0.7 occurred in 28 of 200 readings and 17 of 50 patients. All patients achieved levels below 0.7 nmol/L on at least one reading. Neither age, nor baseline testosterone level significantly predicted either TE1.7 or TE0.7, as shown in Table 3.

PSA levels progressively dropped from an initial median value of 10.4 ng/mL to a median pre-RT PSA level of 0.55. The median PSA halving time was 25 days. Correlations between baseline factors and PSA kinetic outcomes are shown in Table 4. The only significant finding was the baseline PSA level predicted for a lower pre-RT PSA level. The effects of TE0.7 and TE1.7 on PSA

Figure 1. Individual patient PSA levels (nmol/L).

Table 2

Testosterone and PSA response to treatment data.

Variable	Median value (range)
Testosterone, nmol/L	
Baseline	10.3 (1.3–54.1)
6 wk	0.5 (0.1–3.6)
12 wk	0.5 (0.1–8.8)
18 wk	0.5 (0.1–6.0)
24 wk	0.5 (0.1–7.2)
Overall reduction	10.1 (0.4–50.8)
TE, n	
TE1.7	7
TE0.7	17
TE (readings per patient)	
TE1.7	0.19
TE0.7	0.5
PSA, ng/mL	
Baseline	10.4 (1.6–57.0)
6 wk	2.1 (0.56–20.0)
12 wk	0.93 (0.1–27.0)
18 wk	0.65 (0.05–20.0)
24 wk (pre-RT)	0.55 (0.03–14.0)
Overall reduction	9.8 (1.3–49.0)
PSA halving time, d	25 (9–153)

Table 3

Analysis of baseline factors predicting for TE measured at 1.7 and 0.7 nmol/L levels.

	Median (range)	Correlation	p
For TE 1.7			
Age, y	73 (67–75)	−0.113	0.458
Baseline testosterone, nmol/L	9.4 (1.3–54.1)	0.091	0.546
For TE 0.7			
Age, y	73 (58–81)	−0.180	0.241
Baseline testosterone, nmol/L	9.0 (1.3–54.1)	−0.084	0.583

Table 4

Analysis of factors predicting for PSA response.

Variable	Pre-RT PSA level		PSA halving time	
	Correlation	p	Correlation	p
Age	−0.103	0.490	−0.157	0.287
Prognostic risk category	0.264	0.070	0.180	0.216
Gleason score	0.213	0.147	0.046	0.753
Prostate gland volume	−0.069	0.659	−0.128	0.413
Baseline PSA	0.642	<0.001	0.143	0.382
Baseline testosterone	−0.213	0.112	−0.265	0.069

kinetic outcomes are shown in Table 5. The significant findings were that the TE1.7 predicted both a longer PSA halving time and a higher Pre-RT PSA level.

4. Discussion

This study has confirmed that NADT for intermediate- and high-risk prostate cancer patients lowers testosterone to castrate levels in a manner consistent with previous reports about ADT in general.[3] A strength of this study was that the levels were measured in a very frequent and consistent manner, perhaps making TE more likely to be detected. However, the methods for describing TE are not standardized, so comparison with other studies is difficult. The most commonly used cut-off point is 50 ng/dL (1.7 nmol/L) but more modern assays have made more accurate measurements possible and most patients on ADT achieve levels below 20 ng/dL (0.7 nmol/L). In our study, 14% of patients demonstrated TE1.7 and 34% showed TE0.7. There were no factors that significantly predicted for TE, including higher baseline testosterone levels. Although our study used triptorelin, there has been no clear indication from the limited data available that there were any differences in this regard between triptorelin and other ADT medications, or that they were equivalent. Reviews have encountered difficulties in comparing agents as they have been tested in different populations.[1,17] There is at least one study suggesting that in the setting of patients receiving radiotherapy, triptorelin was more effective than the other agents that were tested.[18]

The decline in testosterone was followed by a prompt decline in PSA, with a median halving time of 25 days and leading to a median pre-RT level of 0.55 ng/mL, similar to levels seen in previous reports of NADT, except that nearly all previous reports have had only 3 months of NADT, and one measurement of PSA after the baseline reading.[9] In our study, all patients received NADT for 6 months and had 5 readings.

Relatively few factors have been identified in the literature as having a significant influence on the response to NADT.

The initial PSA level, the suppression of testosterone, African-American race and the use of combined androgen blockade have been shown to affect the PSA response.[19,20] In our study, the only baseline factor significantly associated with a lower pre-RT PSA level was the baseline PSA level. There were no baseline factors that significantly affected the PSA halving time. However, TE at the 1.7 nmol/L occurred in 7 patients after that initiation of treatment and had powerful effects (59.14 vs. 10.01 days, p < 0.01).

Possibilities for further research in this area exist. Other factors that might indicate the response to NADT include the decrease in prostate gland and prostate cancer volumes, and improvements in urinary symptoms. These factors could be compared with the changes in biochemical findings that we have described. These factors, combined with the biochemical factors we have described in this report, indicate a potential to gain improved long-term outcomes by the tailoring of NADT prior to definitive radiotherapy for intermediate and localized prostate cancer. The possibility of tailoring NADT has also been raised in other reports.[21,22] For patients with short PSA halving times, rapidly falling to a stable pre-RT level, it may be beneficial to proceed directly to radiotherapy. For those with a TE, the addition of an anti-androgen or androgen pathway inhibitor may ameliorate the effect on prognosis. For those with higher baseline PSA levels, or longer PSA halving times, where a suitable pre-RT has not yet been reached, prolongation of NADT prior to definitive radiotherapy could be considered, taking into account the additional toxicities and costs. When these individual variations in response to NADT are well understood, prospective trials that compare individualized treatment with standard treatment could be undertaken.

There were some limitations to our study. With only 50 patients, it is a relatively small study, although the a priori sample size was based upon commonly accepted guidelines. The NADT was limited to a single agent and a more powerful effect on the PSA and testosterone levels from a combination with anti-androgens could not be excluded.[19] We did not assess testosterone flare which occurs within a few weeks after initiation of ADT and would require frequent testosterone measurement during that time.

Table 5

Effect of TE on PSA parameters.

	Mean PSA halving time, d	Statistic (ANOVA)	p	Mean Pre-RT PSA, ng/mL	Statistic (ANOVA)	p
TE1.7		19.413	<0.001		18.482	<0.001
Yes	59.14 ± 52.81			4.32 ± 4.39		
No	20.08 ± 10.55			0.77 ± 0.96		
TE0.7		0.838	0.369		0.623	0.434
Yes	30.35 ± 25.41			1.67 ± 2.05		
No	23.10 ± 26.22			1.09 ± 2.57		

Digital rectal examination was not mandated to assess prostate gland volume as it has been shown to be less accurate than imaging methods.[23] The chemiluminescent assay has been considered less accurate than other methods of measuring testosterone for patients receiving ADT.[24] However, these limitations are unlikely to affect the possible conclusions.

To summarize, this is the only existing report that addresses TE in the setting of NADT prior to radiotherapy and one of the most detailed studies of the pattern of decline in PSA levels in that setting. TE at a level of 1.7 nmol/L was associated with longer PSA halving times, suggesting that it may predict an adverse longer-term prostate cancer treatment outcome. Higher baseline PSA levels were associated with higher pre-RT PSA levels. Individualization of NADT, using these and other factors, should be further investigated, as it may improve the effectiveness of the treatment.

Statement of ethics

This project was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Author contributions

All authors were involved in the design of the study, analysis of the data and preparation of the manuscript.

References

[1] Crawford DE, Heidenreich A, Lawrentschuk N, et al. Androgen-targeted therapy in men with prostate cancer: evolving practice and future considerations. *Prostate Cancer Prostatic Dis* 2018;22(1):24–38.

[2] Pieczonka CM, Twardowski P, Renzulli J, et al. Effectiveness of subcutaneously administered leuprolide acetate to achieve low nadir testosterone in prostate cancer patients. *Rev Urol* 2018;20(2):63–68.

[3] Nishiyama T. Serum testosterone levels after medical or surgical androgen deprivation: a comprehensive review of the medical literature. *Urol Oncol* 2014;32(1):38.e17–38.e28.

[4] Pickles T, Hamm J, Morris WJ, Schreiber WE, Tyldesley S. Incomplete testosterone suppression with luteinizing hormone-releasing hormone agonists: does it happen and does it matter? *BJU Int* 2012;110(11 Pt B):E500–507.

[5] Klotz L, O'Callaghan C, Ding K, et al. Nadir testosterone within first year of androgen deprivation therapy (ADT) predicts for time to castration-resistant progression: a secondary analysis of the PR-7 trial of intermittent versus continuous ADT. *J Clin Oncol* 2015;33(10):1151–1156.

[6] Dason S, Allard CB, Tong J, Sheyagan B. Defining a new testosterone threshold for medical castration: results from a prospective cohort series. *Can Urol Assoc J* 2013;7(5–6):e263–e267.

[7] Morote J, Orsola A, Planas J, et al. Redefining clinically significant castration levels in patients with prostate cancer receiving continuous androgen deprivation therapy. *J Urol* 2007;178(4 Pt 1):1290–1295.

[8] Klotz L, Sheyagan B, Guillemette C, et al. Testosterone suppression in the treatment of recurrent or metastatic prostate cancer—a Canadian consensus statement. *Can Urol Assoc J* 2018;12(2):30–37.

[9] Zilli T, Dal Pra A, Kountouri M, Miralbel R. Prognostic value of biochemical response to neoadjuvant androgen deprivation before external beam radiotherapy for prostate cancer: a systematic review of the literature. *Cancer Treat Rev* 2016;46:35–41.

[10] Malik RM, Jani AB, Liauw SL. Prostate-specific antigen halving time while on neoadjuvant androgen deprivation therapy is associated with biochemical control in men treated with radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2011;79(4):1022–1028.

[11] Foo M, Lavieri M, Pickles T. Impact of neoadjuvant prostate-specific antigen kinetics on biochemical failure and prostate cancer mortality: results from a prospective patient database. *Int J Radiat Oncol Biol Phys* 2013;85(2):385–392.

[12] Pinkawa M, Piroth MD, Holy R, et al. Local prostate cancer radiotherapy after prostate-specific antigen progression during primary hormonal therapy. *Radiat Oncol* 2012;7:209.

[13] Cuppone F, Bria E, Giannarelli D, et al. Impact of hormonal treatment duration in combination with radiotherapy for locally advanced prostate cancer: meta-analysis of randomized trials. *BMC Cancer* 2010;10:675.

[14] Heymann JJ, Benson MC, O'Toole KM, et al. Phase II study of neoadjuvant androgen deprivation followed by external-beam radio-therapy with 9 months of androgen deprivation for intermediate to high-risk localized prostate cancer. *J Clin Oncol* 2007;25(1):77–84.

[15] Afriansyah A, Hamid AR, Mochtar CA, Umbas R. Prostate specific antigen (PSA) kinetics as a prognostic factor in metastatic prostate cancer receiving androgen deprivation therapy: systematic review and meta-analysis. *F1000Res* 2018;7:246.

[16] Christie DRH, Sharpley CF. How accurately can prostate gland imaging measure the prostate gland volume? Results of a systematic review. *Prostate Cancer* 2019;2019:6932572.

[17] Bolton E, Lynch T. Are all gonadotrophin-releasing hormone agonists equivalent for the treatment of prostate cancer? A systematic review. *BJU Int* 2018;122(3):371–383.

[18] Wilke D, Patil N, Hollenhorst H, Bowes D, Rutledge R, Ago C. Testosterone suppression with luteinizing hormone-releasing hormone (LHRH) agonists in patients receiving radiotherapy for prostate cancer. *Pharmacotherapy* 2018;38(3):327–333.

[19] Cerne JZ, McGuire SE, Grant SR, et al. Factors associated with improved biochemical response to neoadjuvant androgen deprivation therapy before definitive therapy in prostate cancer patients. *Prostate Cancer Prostatic Dis* 2013;16(4):346–351.

[20] Alexander AS, Mydin A, Jones SO, et al. Extreme-risk prostate adenocarcinoma presenting with prostate-specific antigen (PSA) > 40 ng/ml: prognostic significance of the preradiation PSA nadir. *Int J Radiat Oncol Biol Phys* 2011;81(5):e713–e719.

[21] Alexander A, Crook J, Jones S, et al. Is biochemical response more important than duration of neoadjuvant hormone therapy before radiotherapy for clinically localized prostate cancer? An analysis of the 3- versus 8-month randomized trial. *Int J Radiat Oncol Biol Phys* 2010;76(1):23–30.

[22] McDonald AM, Jacob R, Yang ES, Dobelbower MC, Vanlandingham S, Fiveash JB. PSA response to neoadjuvant androgen deprivation is an independent prognostic marker and may identify patients who benefit from treatment escalation. *Urol Oncol* 2014;32(5):687–693.

[23] Christie D, Windsor J, Sharpley . A systematic review of the accuracy of the digital rectal examination as a method of measuring the prostate gland volume. *J Clin Urol* 2019;12(5):361–370.

[24] Morote J, Comas I, Planas J, et al. Serum testosterone levels in prostate cancer patients undergoing luteinizing hormone-releasing hormone agonist therapy. *Clin Genitourin Cancer* 2018;16(2):e491–e496.