BJUI
BJU International

Long-acting testosterone injections for treatment of testosterone deficiency after brachytherapy for prostate cancer

Felipe G. Balbontin, Sergio A. Moreno, Enrique Bley*, Rodrigo Chacon*, Andres Silva* and Abraham Morgentaler†

*Unidad Urología Clínica Santa María, Santiago, and *Unidad de Urología Hospital del Salvador, Universdad de Chile, Santiago, Chile, and †Men's Health Boston, Harvard Medical School, Boston, MA, USA*

Objective

To evaluate the clinical and biochemical effects of long-acting testosterone undecanoate injections in men with prostate cancer treated with brachytherapy, as the use of testosterone therapy (TTh) in men with prostate cancer is highly controversial, with limited published safety data, particularly after brachytherapy treatment.

Patients and Methods

In all, 20 men treated with brachytherapy for prostate cancer received TTh for symptoms of testosterone deficiency from February 2005 to August 2013. Symptoms of testosterone deficiency included low libido, erectile dysfunction, and fatigue. The mode of TTh was long-acting testosterone undecanoate injections in all cases. Sexual function was assessed by Sexual Health Inventory for Men (SHIM) questionnaire. Serum PSA and testosterone concentrations were recorded monthly for 3 months, then every 3 months for the first year, every 6 months for the second year, and annually then after.

Results

The mean (range) age was 62 (49–74) years and the mean (range) serum PSA level at the time of prostate cancer diagnosis was 6.2 (2–11.5) ng/mL. The Gleason score was 2 + 3 in one patient, 3 + 3 in 15 patients, 3 + 4 in three patients and 4 + 4 in one patient. In all, 15 men were stage T1c and five were T2a. The mean (range) baseline total testosterone concentration was 343 (200–592) ng/dL, and 6.9 (2.1–9.7) ng/dL for free testosterone. The mean SHIM scores improved with treatment from 16.1 at baseline to 22.1 with TTh ($P = 0.002$). There was a decrease in mean PSA level from baseline of 0.7 ng/mL before initiation of TTh to 0.1 ng/mL at last follow-up ($P < 0.001$), with a median (range) follow-up of 31 (12–48) months. There were no cases of prostate cancer progression or recurrence.

Conclusions

With a median of 31-months follow-up, long-acting testosterone injections in men with prostate cancer treated with brachytherapy produced significant clinical benefits. There were no cases of rising serum PSA, prostate cancer progression or recurrence.

Keywords

prostate cancer, brachytherapy, testosterone, hypogonadism

Introduction

Testosterone deficiency, also termed hypogonadism, is a clinical syndrome characterised by symptoms and low levels of serum testosterone. Prominent symptoms of testosterone deficiency include decreased libido, erectile dysfunction, and fatigue. Although there has been increased recognition of the sexual and non-sexual benefits of testosterone therapy (TTh) in testosterone-deficient men, the use of TTh in men with a history of prostate cancer is highly controversial [1].

The controversy about the use of TTh in men with prostate cancer arises from long-established evidence that prostate cancer is androgen-dependent, with the attendant concern that raising serum testosterone may stimulate more rapid prostate cancer growth, thus causing cancer recurrence or progression. For many decades it was uniformly accepted that prostate cancer was an absolute contraindication for the use of TTh, and this position is reinforced by regulatory labelling of testosterone formulations.

 | doi:10.1111/bju.12668
Published by John Wiley & Sons Ltd. www.bjui.org

There is now a limited literature of cases series reporting low rates of prostate cancer progression or recurrence after TTh [1]. The best-studied group consists of men treated with radical prostatectomy (RP). Sarosdy [2] published the only report of TTh after brachytherapy, in 31 men. An additional three brachytherapy cases were included in the report by Pastuszak et al. [3] of 13 men who received TTh after various forms of radiation therapy.

The use of TTh after brachytherapy for prostate cancer raises more concerns than after RP. One reason is the absence of a surgical specimen. Without pathological assessment of the prostate and regional lymph nodes there can be uncertainty about disease extent and stage. A second is that the prostate remains *in situ*, with the possibility that one or more foci of prostate cancer may be suboptimally treated. Finally, serum levels of PSA often fluctuate after brachytherapy and may even increase temporarily in 30–40% of successfully treated men without known cause. This phenomenon, called 'PSA bounce', may cause significant anxiety, as a rise in PSA level is the hallmark of cancer progression [4].

The aim of the present study was to evaluate the clinical and biochemical effects of long-acting testosterone undecanoate injections in a cohort of men with prostate cancer treated with brachytherapy.

Patients and Methods

Between February 2004 and August 2013 we prospectively collected data from men who underwent transperineal, low dose-rate, permanent brachytherapy for early stage prostate cancer. All men were treated at Clínica Santa María, Santiago, Chile using ^{125}I. In this series, we offered TTh to men with characteristic symptoms of testosterone deficiency, primarily symptoms of diminished libido and erectile dysfunction, and with serum free testosterone concentration of <11.7 ng/dL. Initiation of TTh was considered as early as 3 months after brachytherapy, with a requirement for a decline in serum PSA level. Only men with at least 1 year of TTh were included in this study.

The Sexual Health Inventory for Men (SHIM) questionnaire was administered to all men to evaluate erectile function before and after brachytherapy. Other assessments included clinical staging and PSA level at diagnosis and follow-up. Total testosterone was measured at a central laboratory and free testosterone values were obtained by using the online free testosterone calculator (http://www.issam.ch/freetesto.htm). The calculation was performed using measured concentrations of sex hormone binding globulin and a standard value of 4.3 g/dL for albumin [5].

TTh was initiated with 1000 mg testosterone undecanoate i.m. injections, and then adjusted thereafter according to total and free testosterone serum levels, with the objective of achieving a free testosterone concentration of >11.7 ng/dL (normal range: 11.7–18.5 ng/dL). All patients were followed monthly with serum PSA and testosterone concentrations for 3 months, then every 3 months the first year, every 6 months for the second year and annually thereafter. Most patients required one injection per month for 2 months to achieve adequate levels, and were then treated with one injection every 2 months for maintenance.

The 'PSA bounce' phenomenon was defined by an elevation of at least 0.2 ng/mL greater than nadir and subsequent return to nadir levels during the first 24 months [6]. The 'nadir +2 ng/mL' PSA threshold (Phoenix definition) was use to define biochemical relapse. Patients with early rises in PSA level that triggered the Phoenix definition were not considered relapses if subsequent PSA levels declined to <0.5 ng/mL without additional intervention. TTh therapy was withheld in men who had a PSA bounce greater than nadir +2 ng/dL, and was re-instiated only when PSA level returned to nadir levels.

Statistical analyses were performed using the paired Student's *t*-test, with $P < 0.05$ considered to indicate statistical significance.

Results

Of 172 patients treated with brachytherapy 40 received TTh (23%). In this study we analysed the first 20 patients with ≥1 year of follow-up on TTh. Baseline patient characteristics are presented in Table 1. The mean (range) age was 63.5 (49–74) years at time of brachytherapy and the mean serum PSA level was 5.8 ng/mL. The median (range) follow-up after initiation of TTh was 31 (12–48) months.

Gleason score was 2 + 3 in one patient, 3 + 3 in 15 patients, 3 + 4 in three patients and 4 + 4 in one patient. In all, 15 patients were staged as T1c and five as T2a. In all, 19 patients underwent brachytherapy implantation alone, and one patient underwent brachytherapy implantation combined with external-beam radiotherapy due to high risk with a Gleason 4 + 4 tumour.

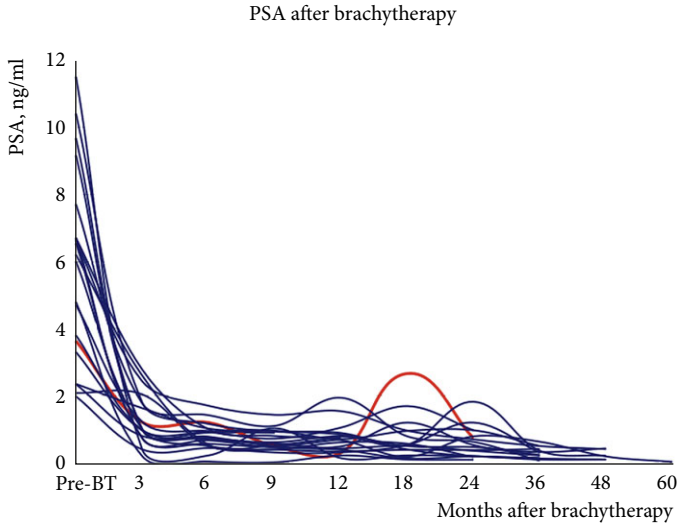
Baseline mean (range) total testosterone was 313 (106–592) ng/dL and free testosterone 6.4 (2.1–11.2) ng/dL. Treatment with testosterone undecanoate injections increased the mean serum testosterone level from 313 to 587 ng/dL (range 330–985 ng/dL; $P < 0.001$) and free testosterone from 6.4 to 14.1 ng/dL (range 8–19.7 ng/dL; $P < 0.001$). The mean (range) time interval between brachytherapy and imitation of TTh was 14 (3–36) months. Treatment with TTh resulted in improved mean SHIM scores from a baseline of 17.8 to 22.1 after TTh ($P = 0.002$).

PSA level results after brachytherapy and initiation of TTh are presented in Figure 1. The PSA level decreased significantly from a baseline mean of 0.7 ng/mL before TTH vs 0.1 ng/mL

Table 1 Study group characteristics before TTH.

Patient no.	Age, years	PSA level, ng/mL	Primary Gleason	Secondary Gleason	Gleason sum	cStage	SHIM score	Total testosterone, ng/dL	Free testosterone, ng/dL
1	68	6.7	2	3	5	T2a	23	220	5.43
2	49	9.7	3	4	7	T1c	25	235	5.82
3	54	6.6	3	3	6	T1c	25	319	8.57
4	64	9.2	3	3	6	T1c	0	180	2.1
5	70	4.7	3	3	6	T1c	14	200	3.72
6	74	11.5	3	3	6	T1c	23	106	8.3
7	72	6.0	3	3	6	T1c	21	211	4.2
8	73	2.4	3	3	6	T2a	17	300	5
9	54	3.3	3	3	6	T1c	22	433	8.09
10	56	6.2	3	3	6	T1c	5	525	9.7
11	72	6.7	3	3	6	T1c	20	290	8.5
12	61	10.4	3	3	6	T1c	23	330	7.85
13	59	7.7	3	3	6	T1c	25	264	5.99
14	62	4.8	4	4	8	T2a	20	250	4.3
15	58	3.8	3	3	6	T2a	25	416	7.52
16	71	2.0	3	3	6	T1c	17	592	5.5
17	59	3.6	3	3	6	T1c	20	486	11.2
18	71	6.5	3	4	7	T1c	9	304	4.23
19	71	2.1	3	4	7	T1c	1	402	6.29
20	51	2.3	3	3	6	T2a	20	200	5
Mean	63.5	5.8		Median	6	Mean	17.8	313.2	6.4

Fig. 1 PSA level after brachytherapy: red arrow shows the only patients with a significant 'bounce', in whom TTh was on hold until the PSA level returned to its nadir. IRB approved protocol number: Santa Maria #12/10290.



at last follow-up ($P < 0.001$). No patient had PSA progression, or development of advanced or metastatic disease.

Several patients had mild PSA level elevations, between 0.1 and 0.3 ng/mL, during the follow-up. Only one patient had a PSA bounce of 2 ng/mL above nadir (Fig. 1). TTh was held until the PSA level returned to its nadir 6 months later, after which TTh was reinstated without any subsequent rise in PSA level until last follow-up. No patient with a mild bounce (<2 ng/mL) had TTh discontinued. In two patients, TTh was discontinued before completing 12 months of TTh due to lack of perceived symptomatic benefit.

Discussion

The present study presents PSA level and prostate cancer outcomes with a median follow-up of >2.5 years in 20 men who received TTh after brachytherapy for prostate cancer. The primary results were that erectile function improved with TTh and no man had prostate cancer progression or recurrence. To our knowledge, this is only the second published report of men who received TTh after brachytherapy for prostate cancer, and the first in which long-acting injections were used for TTh.

The present results confirm the benign experience reported by Sarosdy [2] who first reported the use of TTh in 31 men after brachytherapy. In that study, men were treated with short-acting testosterone cypionate injections for a mean of 4.5 years, with no cases of prostate cancer progression or recurrence. In a report of 13 men who received TTh after various forms of radiation therapy for prostate cancer, Pastuszak et al. [3] included three cases of men who received brachytherapy.

New evidence accumulated over the last 15 years has precipitated re-evaluation of the relationship between prostate cancer and serum androgen concentrations. A large prospective study involving 3886 men with prostate cancer and 6448 men age-matched controls found no relationship between circulating sex hormones and prostate cancer risk [6]. In the placebo arm of the REduction by DUtasteride of prostate Cancer Events (REDUCE) trial in which 3255 men

Table 2 Results of TTh in men with prostate cancer.

Reference	No. of patients	Intervention	Follow-up, months	Gleason score (no. of patients)	Pre-treatment PSA level, ng/mL	Post-treatment PSA level, ng/mL	Pre-treatment testosterone level, ng/dL	Post-treatment testosterone level, ng/dL
Agarwal and Oefelein [12]	10	RP	19	6 (2) 7 (7) 8 (1)	<0.1	<0.1	197	591
Kaufman and Graydon [13]	7	RP	24	6 (6) 7 (1)	<0.1	<0.1	97	434
Khera et al. [14]	57	R	13	≤6 (24) 7 (26) 8 (4)	0.005	0.005	255	459
Pastuszak et al. [10]	103	RP	27.5	<6 (1) 6/7 (72) ≥8 (9)	0.004	0.007	261	460
Sardosdy [2]	31	Brachytherapy	60	5 (3) 6 (19) 7 (6) 8/9 (3)	NA	<0.1	188	489
Morales et al. [15]	5	EBRT	14.5	6 (2) 7 (1) 8 (2)	0.1–0.97	<0.1–1.08	150 (5.2 nmol/L)	507 (17.6 nmol/L)
Pastuszak et al. [3]	13	Brachytherapy and EBRT	29.7	6 (4) 7 (7) 8 (2)	0.3	0.66	172 388	368
Morgentaler et al. [11]	13	AS	30	6 (12) 7 (1)	5.5	3.6	238	664
Morales et al. [15]	6	AS	NA	6 (5) 8 (1)	5.66	NA	259 (9 nmol/L)	NA

AS, active surveillance; EBRT, external beam radiotherapy; NA, not available.

underwent required prostate biopsies at year 2 and 4, no significant relationship was found between serum testosterone or serum dihydrotestosterone and risk of prostate cancer [7].

Although a history of prostate cancer has long been considered a contraindication to the use of TTh [8,9], there are now multiple small to moderately sized case series reporting that TTh does not appear to cause increased risk of prostate cancer progression or recurrence over the short-term (Table 2) [2,3,10–15]. The largest series to date was reported by Pastuszak et al. [10], in which 103 men received TTh after RP, of which 26 were considered high-risk based on the presence of positive surgical margins, Gleason score 8–10, or positive lymph nodes. Results were compared with a group of 49 eugonadal men who underwent RP but did not receive TTh, of which 15 were high-risk. There was biochemical recurrence in 4% of the TTh group compared with 16% of the control group. Morgentaler et al. [11] reported no rise in PSA level or prostate cancer progression with TTh in a group of 13 men on active surveillance for low-risk prostate cancer.

The evidence about the safety of TTh after brachytherapy is limited to one case series of 31 men [2], and a report of 13 men who received TTh after various radiation treatments, of which three were treated with brachytherapy [3]. The results of the present study support and confirm the lack of PSA level or apparent prostate cancer progression in a cohort of men who received TTh after brachytherapy. The present study is the first to show objective data supporting the benefits of TTh with regard to erectile function in this population. SHIM scores increased significantly by 6.0 points, from a baseline of 16.1 to 22.1. Previous studies have shown that a change of 3 points on this scale corresponds to clinical meaningfulness [16]. Additional symptomatic benefits seen in the present study population included increased libido and energy in many men; however, no quantitative assessment was made of those measures.

A primary goal of brachytherapy is to successfully treat the primary cancer while minimising adverse effects, especially with regard to urinary and sexual function. Multiple series indicate that brachytherapy provides a high rate of freedom from biochemical failure at 5 and 10 years, similar to results seen with RP [17–20]. The lack of biochemical failure in the present series with a median follow-up of >2.5 years is reassuring given published 5-year biochemical failure rates of 10% to 25%.

One issue of particular concern in men treated with brachytherapy is the 'PSA bounce', referring to the transient rise in PSA levels that occurs in nearly 25% of men [6] before reaching a true nadir at 24–36 months. Given the longstanding concerns about the potential of TTh to cause more rapid

prostate cancer growth [8,9], the occurrence of any increase in PSA level seen with TTh is likely to be interpreted as due to androgenic stimulation of residual prostate cancer [21]. In the present series, we present our management of TTh in men after brachytherapy for prostate cancer. In the present series, we considered the use of TTh in men who had characteristic symptoms of testosterone deficiency, especially symptoms of diminished libido and erectile dysfunction, and a serum free testosterone of < 11.7 ng/dL. Initiation of TTh was started as soon as 3 months after implantation as long as a decline in PSA level was seen. In addition, we present our management of 'PSA bounce' in these men receiving TTh after brachytherapy, in which testosterone injections are held until PSA levels return to baseline. Re-initiation of TTh failed to elicit a rise in PSA level (shown as a red line in Fig. 1).

The present report is also the first to describe the use of long-acting testosterone injections in men with a history of prostate cancer. One theoretical concern with such treatment is that androgenic stimulation of residual viable prostate cancer cells would be more difficult to treat with long-acting testosterone preparations. This was not a problem in the present series.

The present study has several important limitations, including small size of the study population, modest duration of follow-up, retrospective methodology, and lack of objective measures for symptoms of hypogonadism, such as low libido and fatigue. However, we feel that the present report adds significantly to the existing literature, which lacks any controlled prospective studies, and is particularly limited with regard to the brachytherapy population.

In conclusion, we found a significant improvement in sexual function in men who received TTh for a median of 2.5 years after brachytherapy for prostate cancer, without any cases of prostate cancer progression or recurrence. This report adds to the limited literature suggesting that TTh may be reasonably offered to selected men with prostate cancer after definitive treatment.

Conflicts of Interest

S.A.M. has received occasional financial support from Bayer as a speaker or to attend conferences in relation to this work.

A.M. reports grants and personal fees from Auxilium, grants and personal fees from Antares, grants from Lilly, personal fees from Bayer, personal fees from Merck, during the conduct of the study; and personal fees from Abbvie outside the submitted work.

All other authors have no conflicts to disclose.

References

1 **Khera M, Crawford D, Morales A, Salonia A, Morgentaler A.** A new era of testosterone and prostate cancer. From physiology to clinical implications. *Eur Urol* 2014; 65: 115–23

2 **Sarosdy MF.** Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. *Cancer* 2007; 109: 536–41

3 **Pastuszak AW, Pearlman AM, Godoy G, Miles BJ, Lipshultz LI, Khera M.** Testosterone replacement therapy in the setting of prostate cancer treated with radiation. *Int J Impot Res* 2013; 25: 24–8

4 **Caloglu M, Ciezki J.** Prostate-specific antigen bounce after prostate brachytherapy: review of a confusing phenomenon. *Urology* 2009; 74: 1183–90

5 **Vermeulen A, Verdonck L, Kaufman JM.** A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab* 1999; 84: 3666–72

6 **Roddam AW, Allen NE, Appleby P, Key TJ, Endogenous Hormones Prostate Cancer Collaborative Group.** Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J Natl Cancer Inst* 2008; 100: 170–83

7 **Muller RL, Gerber L, Moreira DM, Andriole G, Castro-Santamaría R, Freedland SJ.** Serum testosterone and dihydrotestosterone and prostate cancer risk in the placebo arm of the reduction by dutasteride of prostate cancer events trial. *Eur Urol* 2012; 62: 757–64

8 **Huggins C, Hodges CV.** Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res* 1941; 1: 293–7

9 **Huggins C, Stevens RE Jr, Hodges CV.** Studies on prostatic cancer. II. The effects of castration on advanced carcinoma of the prostate gland. *Arch Surg* 1941; 43: 209–23

10 **Pastuszak AW, Pearlman AM, Lai WS et al.** Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. *J Urol* 2013; 190: 639–44

11 **Morgentaler A, Lipshultz LI, Bennett R, Sweeney M, Avila D Jr, Khera M.** Testosterone therapy in men with untreated prostate cancer. *J Urol* 2011; 185: 1256–60

12 **Agarwal PK, Oefelein MG.** Testosterone replacement therapy after primary treatment for prostate cancer. *J Urol* 2005; 173: 533–6

13 **Kaufman JM, Graydon RJ.** Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. *J Urol* 2004; 172: 920–2

14 **Khera M, Grober ED, Najari B et al.** Testosterone replacement therapy following radical prostatectomy. *J Sex Med* 2009; 6: 1165–70

15 **Morales A, Black AM, Emerson LE.** Testosterone administration to men with testosterone deficiency syndrome after external beam radiotherapy for localized prostate cancer: preliminary observations. *BJU Int* 2009; 103: 62–4

16 **Tuncel A, Nalcacioglu V, Ener K, Aslan Y, Aydin O, Atan A.** Sildenafil citrate and tamsulosin combination is not superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. *World J Urol* 2010; 28: 17–22

17 **Blasko JC, Grimm PD, Sylvester JE, Badiozamani KR, Hoak D, Cavanagh W.** Palladium-103 brachytherapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys* 2000; 46: 839–50

18 **Ragde H, Elgamal AA, Snow PB et al.** Ten-year disease free survival after transperineal sonography-guided iodine-125 brachytherapy with or without 45-gray external beam irradiation in the treatment of patients with clinically localized, low to high Gleason grade prostate carcinoma. *Cancer* 1998; 83: 989–1001

19 **Bianco FJ Jr, Scardino PT, Eastham JA.** Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ('trifecta'). *Urology* 2005; 66 (Suppl.): 83–94

20 **Hull GW, Rabbani F, Abbas F, Wheeler TM, Kattan MW, Scardino PT.** Cancer control with radical prostatectomy alone in 1000 consecutive patients. *J Urol* 2002; 167: 528–34

21 **Morales A, Schulman CC, Tostain J, Wu FC.** Testosterone deficiency syndrome (TDS) needs to be named appropriately – the importance of accurate terminology. *Eur Urol* 2006; 50: 407–9

Correspondence: Felipe G. Balbontin, AV. Santa Maria, 0500, Providencia, Santiago, Chile.

e-mail: fbalbontin@gmail.com

Abbreviations: RP, radical prostatectomy; SHIM, Sexual Health Inventory for Men; TTh, testosterone therapy.