



## Testosterone Profiles After Brachytherapy for Localized Prostate Cancer

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<b>OBJECTIVE</b>	To evaluate patients' serum total testosterone levels (STLs) after brachytherapy (BT) for prostate cancer.
<b>METHODS</b>	We enrolled 102 men who underwent permanent interstitial BT using I <sup>125</sup> without androgen deprivation therapy for localized prostate cancer. Seed BT radiation dose was 145 Gy. Patients were followed for 24-60 months after BT. The primary outcome was STL kinetics after BT. Predictors of testosterone decrease were also analyzed.
<b>RESULTS</b>	Median preimplantation STL was 4.18 ng/mL. STL decreased significantly to a median nadir of 89.4% of baseline (3.72 ng/mL) occurring at 6 months, and then recovered to baseline at 18 months after BT. The group of patients whose STLs fell below 3.00 ng/mL (biochemical hypogonadism) after BT started with lower baseline STLs (median: 3.54 ng/mL) than patients whose STLs did not fall below 3.00 ng/mL (median: 4.90 ng/mL). The group of patients whose STLs decreased by more than 1.00 ng/mL over the study period had significantly higher median baseline STLs (median: 5.05 ng/mL) than the group whose STLs decreased by less than 1.00 ng/mL (median: 3.64 ng/mL).
<b>CONCLUSION</b>	Although STL decreased significantly after I <sup>125</sup> -based BT, STL decline after treatment for localized prostate cancer was not large and recovered over time. UROLOGY 126: 121–127, 2019. © 2019 Elsevier Inc.

Prostate cancer (PCa) is common in older men, and the lifetime risk of developing PCa is 15.3% in men in the United States.<sup>1</sup> Radiation therapy (RT) is a definitive treatment for PCa and approximately 25% of PCa cases are treated with RT.<sup>2</sup> Brachytherapy (BT) is type of RT modality and an established therapy for PCa, in which low- or high-dose radioactive sources are implanted into prostate tissue. The National Comprehensive Cancer Network (NCCN) guidelines recommend BT as a monotherapy for low-risk PCa, and a combination of BT together with external-beam RT (EBRT) for high-risk or locally advanced PCa.<sup>3</sup> For low-risk PCa, the efficacy of BT is comparable to radical prostatectomy.<sup>3</sup> Recent studies on the efficacy of androgen deprivation

therapy (ADT) in conjunction with RT found that long-term ADT improved overall survival in high-risk PCa patients.<sup>4</sup> Therefore, long-term ADT before and during RT is recommended for high-risk PCa patients.<sup>5</sup> However, the potential for adverse effects of ADT with regard to testosterone deficiency (TD) for these patients has not been completely determined.

TD impairs the functions of multiple organs, which can lead to depression, erectile dysfunction, metabolic syndrome, and lower quality of life.<sup>6</sup> Some studies have reported TD after RT, even in patients who did not receive ADT.<sup>7-9</sup> Therefore, as long-term survival becomes increasing likely for men who undergo treatment for localized PCa,<sup>10</sup> clarifying the changes in serum total testosterone level (STL) after RT for PCa is necessary for optimal informed consent and long-term follow-up.

Over half of the studies that examined changes in STL after RT without ADT (using EBRT, intensity-modulated RT, CyberKnife, and Pd<sup>103</sup>-based BT) showed some degree of STL decline after RT.<sup>7,8,11</sup> However, to the best of our knowledge, no study has yet investigated STL kinetics after I<sup>125</sup>-based BT for localized PCa. In this study, we evaluated STLs over time after I<sup>125</sup>-based BT without ADT in patients with localized PCa.

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## METHODS AND MATERIALS

We retrospectively evaluated records of 102 patients who underwent permanent interstitial BT from October 2007 to January 2015 and met both the inclusion and exclusion criteria for this study. The interstitial I<sup>125</sup>-based BT seeds were implanted by a single brachytherapist at our medical center. Details of preplanning methods, intraoperating approach and dosimetric evaluations were done according to Nag et al.<sup>12</sup>

Patients were enrolled in the study if they met the following criteria: (1) they had undergone only BT for localized PCa; (2) they had not received neoadjuvant or adjuvant ADT; and (3) STL was measured using the same assay pretreatment and post-treatment and followed for at least 24 months after BT.

We excluded patients who underwent BT for salvage treatment with biochemical recurrence. Decisions to undergo BT therapy were based on the oncologists' judgment and patients' informed consent. None of the patients protected their testes during BT or had adjuvant therapy because of biochemical recurrence.

STLs were measured before BT and 1, 3, 6, and every 6 or 12 months after BT using a chemiluminescent immunoassay; assays were performed, at various times of the day by a single laboratory on a single machine, ARCHITECT i2000SR (Abbott Diagnostics, Abbott Park, Tokyo, Japan). Serum prostate-specific antigen (PSA) levels were also measured before and after BT.

We retrospectively analyzed patients' baseline characteristics, clinical parameters, and total STLs before BT and up to 60 months after BT using our maintained database. Primary outcomes were STL profiles after BT. We also analyzed predictors of testosterone decrease from baseline patients' characteristics. Biochemical hypogonadism was defined as STL <3.00 ng/mL according to the guidelines of the American Urological Association.<sup>13</sup> The patients' database was registered with our institutional ethical committee. This study was conducted in accordance with the Declaration of Helsinki.

Data are presented as median values (interquartile range [IQR]). Differences in STLs were determined using a 2-sided paired *t* test. Multivariate logistic regression analyses were used to evaluate relationships between risk variables and STLs. We excluded patients who had hypogonadism (STL <3.00 ng/mL) before treatment from the univariate and multivariate analyses of testosterone decrease. *P* <0.05 was considered significant.

## RESULTS

Table 1 presents the baseline characteristics of the 102 patients who were included in this study. No patients had undergone testosterone replacement therapy (TRT) before or after BT. Changes in STLs are shown in Figure 1. The median pretreatment STL for the entire cohort was 4.18 ng/mL (IQR: 3.35-5.21). Although the median STL at 1 month after BT (4.29 ng/mL; IQR: 3.56-5.28) was not significantly different from median pretreatment STL, the median STL at 3 months after BT (3.73 ng/mL; IQR: 2.97-4.61) was significantly decreased compared with pretreatment STL (*P* <.001). The median STL nadir occurred at 6 months after BT (3.72 ng/mL; IQR: 3.02-4.69, *P* <.001, ES: *d* = 0.46, (1-β) = 0.50) at 89.4% (median) of pretreatment STL and recovered gradually until at 18 months after BT, at which point the median STL (3.98 ng/mL; IQR: 3.08-5.16) did not significantly differ from pretreatment STL. The median STL also did not significantly differ at 24 months (4.08 ng/mL; IQR: 3.41-5.10), 36 months (4.26 ng/mL; IQR: 3.63-5.12), 48 months (4.33 ng/mL;

**Table 1.** Baseline characteristics of patients treated with brachytherapy (*n* = 102)

Continuous	Median	(IQR)
Age (y)	70.5	(66.0–74.0)
Follow-up period (mo)	48	(48.0–60.0)
Preimplant PSA (ng/mL)	6.7	(4.8-8.7)
Preimplant testosterone (ng/mL)	4.18	(3.35–5.21)
Prostate volume (mL)	26.6	(22.0–29.6)
BMI (kg/m <sup>2</sup> )	23.4	(21.8–25.3)
Categorical (located middle) gray back ground	Number (middle) gray back ground	(%) (Middle) gray back ground
Gleason score		
5	3	2.9
6	40	39.2
7	59	57.8
Clinical stage		
T1c	79	77.5
T2a	17	16.7
T2b	5	4.9
Hypertension		
Yes	47	46.1
No	55	53.9
Dyslipidemia		
Yes	6	5.9
No	96	94.1
Diabetes mellitus		
Yes	10	9.8
No	92	90.2
Coronary artery disease		
Yes	19	18.6
No	83	81.4

BMI, body mass index; IQR, interquartile range; PSA, prostate-specific antigen.

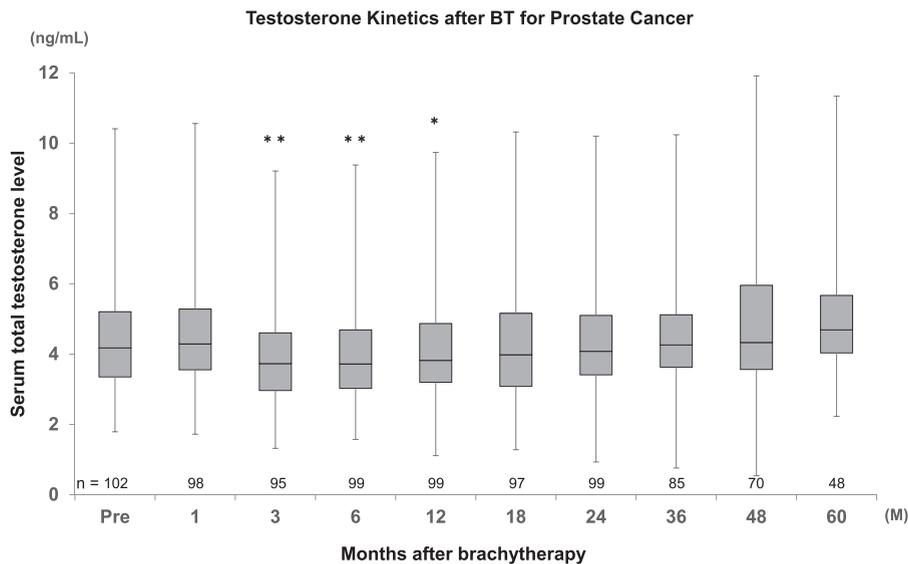
IQR: 3.56-5.96) and 60 months after pretreatment STL (4.69 ng/mL; IQR: 4.03-5.67).

A total of 14 (12.7%) patients had a pretreatment STL <3.00 ng/mL (ie, hypogonadism), and these patients were excluded from analyses of testosterone decrease predictors. Among the remaining 89 patients, 27 (30.3%) had STLs that decreased to <3.00 ng/mL after BT; these patients tended to have lower (but not hypogonadal) pretreatment STLs (median: 3.54 ng/mL; IQR: 3.34-3.95). The remaining 62 (69.7%) patients with STLs that did not fall below 3.00 ng/mL tended to have higher pretreatment STLs (median: 4.90 ng/mL; IQR: 4.09-5.93). The group of patients whose STLs decreased by more than 1.00 ng/mL over the study period had significantly higher median baseline STLs (median: 5.05 ng/mL; IQR: 4.22-6.15) than did the group whose STLs decreased by less than 1.00 ng/mL (median: 3.64 ng/mL; IQR: 3.33-4.37; Table 2).

Serum PSA kinetics did not parallel with STLs. The median serum PSA was significantly decreased at 1 month after BT compared with pretreatment (*P* <.001, paired *t* test) and continued to decrease until 60 months after BT (Supplementary Fig. S1).

## DISCUSSION

TD can cause erectile problems, depression, and fatigue. Long-term TD may cause poor organ function related to reduced muscle mass and bone density and increased fat



**Figure 1.** Testosterone kinetics after brachytherapy for patients with localized prostate cancer.

**Serum total testosterone levels over time after brachytherapy for patients with localized prostate cancer, represented by box-and-whisker plot. Not all patients contributed to all the time points. STLs at 3, 6, and 12 months after brachytherapy were significantly decreased from pretreatment levels. \* $P < .05$ , \*\* $P < .01$  (paired  $t$  test).**

mass.<sup>6</sup> Although TD incidence increases with age, TD may also occur after RT. Some studies reported TD after RT even in patients who did not receive ADT.<sup>7-9</sup> Because PCa patients may now survive long after treatment,<sup>10</sup> their post-RT STLs warrant consideration.

This study evaluated testosterone changes after BT in men with localized PCa who did not receive ADT. The median follow-up period was 48 months, and all patients underwent BT monotherapy. We found that STL decreased significantly at 3 months after BT compared with pretreatment levels and reached its lowest point at about 6 months after BT. STL then recovered gradually to the pretreatment level by 18 months after BT. The median lowest STL (3.72 ng/mL; IQR: 3.02-4.69; 89.4% of median baseline) did not reach biochemical hypogonadism.

After the 2017 review by Nichols et al that included 8 papers on serum testosterone kinetics after RT for PCa since 1990,<sup>14</sup> 2 more reports, including this current study, were reported (Table 3). The number of patients in each of these studies varied from 26 to 666. Although most of these studies included patients with low- or intermediate-risk PCa or patients with localized PCa, a study by Pickles et al included patients with locally advanced disease.<sup>8</sup> No patients in these studies received any neoadjuvant or adjuvant ADT, and their RT modality and dosing varied. The testicles were protected in only 1 study (Daniell et al) by a precise collimator and customized blocking of the radiation beam.<sup>15</sup> Follow-up periods ranged from 3 to 96 months. Seven of the 10 studies reported some degree of STL decline after RT. Although the study from Daniell et al reported lower STL in patients treated with RT compared with patients treated with radical prostatectomy at 3-8 years post-treatment,<sup>15</sup> other studies reported that

STL declined to 70%-91% of pretreatment levels within 1 year after RT. The most recent study, from Pompe et al, reported that 75% of 248 patients treated with EBRT monotherapy showed decreased STL (median time to first decrease: 6.4 months; median decrease at nadir: 30% of baseline). In their study, 45% of patients developed biochemical hypogonadism. However, of all the patients with decreased STL, 63% recovered to at least 90% of baseline.<sup>7</sup> Although the clinical significance is unclear, these results show that STL can decrease after RT.

Only 1 report on testosterone kinetics after BT for PCa patients is available. Taira et al reported on testosterone changes of 221 patients who underwent BT using Pd<sup>103</sup> without ADT for localized PCa. In this study, 41% (90/221) of patients received various doses of supplemental EBRT. The authors measured STL preimplantation, 3 months postimplantation and every 6 months thereafter, and found no significant increase or decrease in STL at 27 months postimplantation. The patients were encouraged to have STL drawn in the morning, but STL was measured in different regions using different testosterone assays. Therefore, values from different assays were normalized to the most common test. Among these patients, 29% experienced an increase in STL of  $\geq 25\%$ , 23% of patients experienced a decrease in STL of  $\geq 25\%$ , and the remaining 48% had no notable change in STL over time.<sup>16</sup>

To the best of our knowledge, the current study is the first report on testosterone kinetics after I<sup>125</sup>-based BT. We also observed that STL declined after BT without ADT for patients with localized PCa, but the median STL decline from baseline was 10.6%, and STL had recovered by 18 months.

The etiology of TD after RT has been postulated to reflect decreased STL caused by scattered radiation to the

**Table 2.** Factors thought to influence change in serum testosterone levels after brachytherapy

Median (IQR)/Number (+/-)	TT ≤3.00 ng/mL			TT Decrease ≥1.00 ng/mL			P Value	95%CI	OR	P Value
	+(n = 27)	-(n = 62)		+(n = 50)	-(n = 39)					
Age (y)	70.0 (66.0-73.0)	71.0 (67.3-75.0)		71.0 (67.0-73.0)	71.0 (67.0-74.0)		.45	0.87-1.07	0.96	0.98
Preimplant testosterone (ng/mL)	3.54 (3.34-3.95)	4.90 (4.09-5.93)		5.05 (4.22-6.15)	3.64 (3.33-4.37)		<.001	0.13-0.52	0.26	2.98
Prostate volume (mL)	23.6 (21.2-29.3)	26.7 (23.5-29.6)		26.7 (23.5-30.3)	25.9 (21.1-29.2)		.34	0.87-1.05	0.96	1.02
BMI (kg/m <sup>2</sup> )	24.2 (22.7-25.2)	23.3 (21.5-25.4)		23.3 (21.3-25.4)	23.7 (22.4-25.1)		.68	0.77-1.12	0.96	0.95
Hypertension	12/15	26/36		22/28	16/23		.43	0.50-5.13	1.59	1.24
Dyslipidemia	2/25	3/59		1/49	4/35		.85	0.83-7.70	0.80	0.29
Diabetes mellitus	1/26	5/57		2/48	4/35		.16	0.01-2.04	0.17	0.87
Coronary artery disease	5/22	9/53		8/42	6/33		.70	0.16-3.38	0.74	0.75

testes, leading to Leydig cell dysfunction and thus less testosterone. In a study of EBRT by Pickles et al, the authors found that patients with low preintervention STLs and those treated with larger radiation volumes had lower testosterone nadirs.<sup>8</sup> While several EBRT studies measured scattered testicular radiation doses of ~200 cGy,<sup>8,17-19</sup> Mydlo et al estimated testicular doses at ~19 cGy in men treated with I<sup>125</sup>-based BT.<sup>20</sup> In their study, postimplantation semen analysis of 4 young patients did not significantly differ from preimplantation levels. However, the authors did not evaluate STL changes after BT. Taira et al estimated the proximal testicular dose to be ~2 cGy over the life of a Pd<sup>103</sup> implant.<sup>16</sup> The 27-month follow-up study showed no significant STL decline after implantation, even for patients who received 20-45 Gy supplemental EBRT. The authors therefore concluded that a very low radiation scatter dose to the testes did not affect STL after BT.<sup>16</sup> The present study was not designed to estimate the testicular radiation dose after BT or uncover the mechanism of STL decline, which might include stress responses to treatment.<sup>21</sup>

The only factor that appeared to influence STL change after BT was pretreatment STL (Table 2). From logistic regression analysis, we found that patients whose STLs decreased to below 3.00 ng/mL (ie, biochemical hypogonadism) after treatment tended to have lower pretreatment STLs (median: 3.54 ng/mL), and the median STL decrease from pretreatment to nadir was 31.9%, whereas patients whose STLs did not decrease below 3.00 ng/mL tended to have higher pretreatment STLs (median: 4.90 ng/mL). Patients whose STLs decreased by more than 1.00 ng/mL over the study period had significantly higher median baseline STLs (median: 5.05 ng/mL) than the group whose STLs decreased by less than 1.00 ng/mL (median: 3.64 ng/mL), with a median STL decrease of 35.0% from pretreatment to nadir. These findings are in agreement with previous reports.

The EBRT study of Pickles et al reported that low baseline STL predicted a lower testosterone nadir, and greater STL decline was found in patients with higher baseline STLs.<sup>8</sup> Taira et al also concluded that prostate BT did not appear to affect STL over time, but the sub-analysis showed that baseline STL was the predictor for change in STL over time. The patients with higher-than-average baseline STL tended to experience significant STL decline, whereas patients with average or below average baseline STL showed no significant changes.<sup>16</sup> The reason for this phenomenon is unclear.

The patients' baseline characteristics should also be considered. High body mass index (≥25 kg/m<sup>2</sup>) and history of hypertension, hyperlipidemia, and/or diabetes have been associated with hypogonadism.<sup>22</sup> The hypogonadism in males (HIM) study reported that approximately 35% of older patients in the US were hypogonadal at baseline. In the current study, only 12.5% of enrolled patients had pretreatment STL <3.00 ng/mL (ie, hypogonadism). Compared with the HIM study, the percentages of our patients with these risk factors for hypogonadism

**Table 3.** Studies of testosterone kinetics after radiation therapy for prostate cancer

Author	Year	Patient Number	Inclusion Criteria	ADT (+/–)	Modality	Dose (Gy)	Testicular Shield (+/–)	Follow-up Period (mo)	Time of Sample Taken	STL Decline After RT		
										(+/-)	Evaluation Time After RT (mo)	Ratio From Baseline (%)
Pompe	2017	248	Localized PCa	–	3D-CRT /IMRT	70-79	–	69 (median)	NR	+	6.4 (first decrease)	30
Nichols	2017	371	Localized PCa SA ≤ 20 ng/mL	–	2D-EBRT /3D-CRT	66.6-68.4	NR	3	NR	+	3	9.3
Kil	2013	217	Low-, intermediate-risk PCa	–	Protons	70-72.5 (CGE)	NR	24 (median)	NR	–		
Taira	2012	221	Localized PCa	–	Pd <sup>103</sup> BT ± EBRT	NR	NR	27	encouraged in the morning	–		
Nichols	2012	150	Low-, intermediate-risk PCa	–	Protons	78-82	NR	24	NR	–		
Oermann	2011	26	Low-, intermediate-risk PCa	–	CyberKnife SBRT	36.25	–	15 (median)	in the morning and early afternoon	+	12	23.8
Pickles	2002	666	PCa TT ≥ 5nmol/l	–	3D-CRT	52.5-70	–	39 (median)	Various times of the day	+	6	17
Daniell	2001	33	Localized PCa	–	2D-EBRT	115	+	36-96	NR	+	36-96	27.3 vs surgery
Zagars	1997	85	Localized PCa	–	2D-EBRT	66-70	NR	3	NR	+	3	9
Current study	2018	102	Localized PCa	–	<sup>125</sup> I BT	145	–	60	Various times of the day	+	6	10.6

2D, 2-dimensional; 3D, 3-dimensional; ADT, androgen deprivation therapy; BT, Brachytherapy; CGE, cobalt gray equivalent; CRT, conformal radiation therapy; EBRT, external beam radiation therapy; IMRT, intensity-modulated radiation therapy; NR, not recorded; PCa, prostate cancer; PSA, prostate specific antigen; RT, radiation therapy; STL, serum total testosterone level.

were low, even when compared with eugonadal patients in the HIM study.<sup>22</sup> Moreover, general stress associated with cancer treatment may have a greater effect on active men with higher STL.

Patients with TD after RT may receive TRT. Although TRT has been historically contraindicated for PCa patients because of the risk of cancer growth,<sup>23</sup> in recent years, understanding of the relationship between STL and PCa development has shifted.<sup>24</sup> Although studies are limited, the review by Kaplan et al indicated that patients who received TRT after EBRT or BT for localized PCa do not appear to suffer higher rates of recurrence or worse outcomes compared with those who did not receive TRT.<sup>24-26</sup> Nguyen et al also found that TRT is safe and effective for hypogonadal men with low- or intermediate-risk PCa.<sup>27</sup> Vignozzi et al reported that TD, rather than TRT, affected PCa progression because of inflammation caused by TD.<sup>28</sup> Martin et al reported that higher Gleason scores were associated with shorter time to testosterone normalization after 6 months of combined androgen blockade and RT, and the authors hypothesized that a factor released from high-grade PCa cells may affect testosterone production.<sup>29</sup> These reports suggest that TRT is safe for patients with TD after RT for low-grade localized PCa.

This study excluded both patients who underwent salvage BT for biochemical recurrence, and those who suffered biochemical recurrence during the study period. As described above with TRT, the correlation between STL change and biochemical recurrence is unclear. However, STL kinetics after RT are reportedly unrelated to biochemical recurrence.<sup>7,8</sup> Our results also demonstrated that serum PSA kinetics did not parallel STLs.

This study had several limitations. First, STLs were not measured before patients were diagnosed with PCa. Because the psychological stress of a PCa diagnosis could negatively affect STLs, postdiagnosis STLs might be lower than the patient's actual baseline. Second, STL was measured at various times of the day, and not controlled with morning-only draws. STL varies with circadian rhythm, and is typically higher in the morning, and lower in the afternoon. However, this diurnal fluctuation is less apparent in elderly men.<sup>30</sup> Third, we did not include a validated questionnaire on symptoms related to RT for PCa, and thus we did not fully assess the relationship between TD and health-related quality-of-life. Fourth, long-term changes in total STL over a patient's lifetime are unclear, including the likelihood of TD and its clinical symptoms going forward. To address these limitations, a larger, long-term prospective study is necessary.

## CONCLUSION

We found that the effect of I<sup>125</sup>-based BT for localized PCa on total STL is mostly temporary, with a median low point of 89.4% of baseline occurring at about 6 months post-BT that gradually recovers until about 18 months post-BT. Patients with low baseline STLs tended to decrease to biochemical hypogonadism after treatment,

whereas those with high baseline STLs tended to decrease to a higher range. This is the first report to evaluate STL changes after I<sup>125</sup>-based BT.

## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urology.2019.01.022>.

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