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Serum Testosterone 60 Months after Passive-Scatter Proton Therapy for Localized Prostate Cancer

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ABSTRACT

Studies demonstrate a decline of ~10% in serum testosterone (ST) level after X-ray radiotherapy for prostate cancer. We evaluated changes in ST for patients with low- and intermediate-risk prostate cancer receiving 70-82Gy(RBE) using passive-scatter proton therapy (PT). ST was checked at baseline ($n = 358$) and at 60+ months after PT ($n = 166$). The median baseline ST was 363.3 ng/dl (range, 82.0–974.0). The median ST 5 years after PT was 391.5 ng/dl (range, 108.0–1061.0). The difference was not statistically significant ($p = 0.9341$). Passive-scatter PT was not associated with testosterone suppression at 5 years, suggesting that protons may cause less out-of-field scatter radiation than X-rays.

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Serum testosterone; Bladder and prostate cancer; Proton therapy; Radiation oncology

Introduction

In 1997, Zagars and Pollack (1) published a report evaluating changes in serum testosterone (ST) levels for 85 patients treated with external-beam radiotherapy (EBRT) for localized prostate cancer. At 3 months of follow-up, the study demonstrated a statistically significant 9% decline in ST. Since that publication, seven additional studies have confirmed declines in ST in this setting (2–8). The current consensus among these authors is that the decline in ST is a function of scatter radiation dose delivered to the testicular Leydig cells.

Two additional studies for patients treated with passive-scatter proton therapy (PT) on three prospective studies have failed to demonstrate such decline in ST with up to 24 months of follow-up (9, 10). The current series reviews changes in ST for the above patients who now have a minimum 5 years of follow-up.

Materials and methods

Between August 2006 and October 2011, 399 patients with low- and intermediate-risk prostate cancer were enrolled on three prospective institutional review board-approved trials delivering between 70 Gy(RBE) and 82 Gy(RBE) at between 2 and 2.5 Gy(RBE) per fraction using PT. The details of these trials have been previously published (11, 12).

ST was to be checked at baseline and every 6 months after PT. In total, 358 eligible patients were available for analysis. The analysis excluded the following patients: 6 without baseline ST; 6 without reliable post-PT testosterone data; 14 with pre-PT LHRH agonist therapy; 2 with pre-PT testosterone supplementation; and 13 were withdrawn because of protocol (dose) deviations.

Data were analyzed with JMP software (SAS Institute, Cary, NC, USA). A matched-pair comparison of 5-year ST levels to baseline was accomplished with the non-parametric Wilcoxon signed rank test.

Results

The median baseline ST level for all 358 evaluable patients was 363.3 NG/DL (mean, 380.4 NG/DL).

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Table 1. Serum testosterone levels for all patients enrolled in the PR01, PR02, and PR04 protocols.

Month	No. of patients	Median NG/DL	Mean NG/DL	Median Δ	*p* Value
Baseline	358	363	380	N/A	N/A
6	319	364	384	1%	0.021
12	297	355	379	1%	0.1004
18	249	365	379	−1%	0.3624
24	259	338	368	−3%	0.8616
30	232	370	385	−4%	0.6366
36	183	363	377	−3%	0.6619
42	127	374	377	−4%	0.8323
48	162	375	385	−7%	0.344
54	82	352	377	−6%	0.2183
60	166	392	395	0%	0.5242

N/A: not applicable.

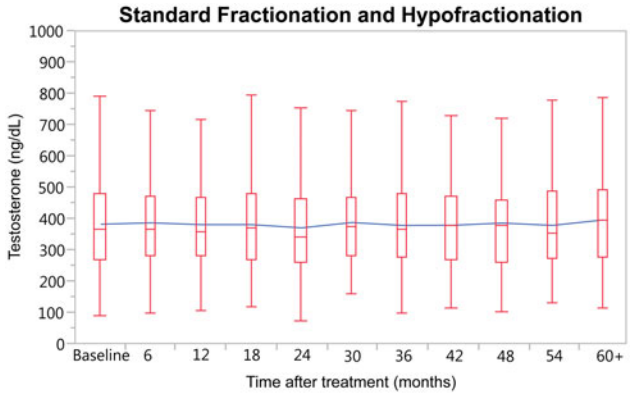

Figure 1. Testosterone concentration across time for all patients enrolled on three of our institution's protocols: standard fractionation (PR01 and PR02) and moderate hypofractionation (PR04).

The median ST level 5 years after PT was 391.5 NG/DL (mean, 394.7 NG/DL). The difference was not statistically significant ($p = 0.9341$). The data are shown in 6-month intervals in Table 1 and Figure 1.

The median baseline ST for the 154 evaluable patients treated with standard 2 Gy(RBE) fractionation was 355.8 NG/DL (mean, 373.5 NG/DL). Median ST level 5 years after PT was 391.5 NG/DL (mean, 387.9 NG/DL). The difference was not statistically significant ($p = 0.9683$). The data are shown in 6-month intervals in Table 2 and Figure 2.

The median baseline ST level for the 204 evaluable patients treated with moderate 2.5 Gy(RBE) hypofractionation was 368.8 NG/DL (mean, 385.6 NG/DL). Median ST level 5 years after PT was 391.5 NG/DL (mean 405.7). The difference was not statistically significant ($p = 0.9001$). The data are shown in 6-month intervals in Table 3 and Figure 3.

Table 2. Serum testosterone levels for all patients treated with standard fractionation and enrolled in PR01 and PR02.

Month	No. of patients	Median NG/DL	Mean NG/DL	Median Δ	*p* Value
Baseline	154	356	374	N/A	N/A
6	139	365	385	5%	0.0094
12	130	346	370	0%	0.1971
18	102	348	363	−1%	0.7117
24	104	329	353	−10%	0.2611
30	101	357	371	−5%	0.9638
36	80	349	364	−4%	0.6897
42	47	327	357	−2%	0.8923
48	82	378	384	−2%	0.3087
54	33	335	370	−12%	0.3469
60	102	392	388	0%	0.4306

N/A: not applicable.

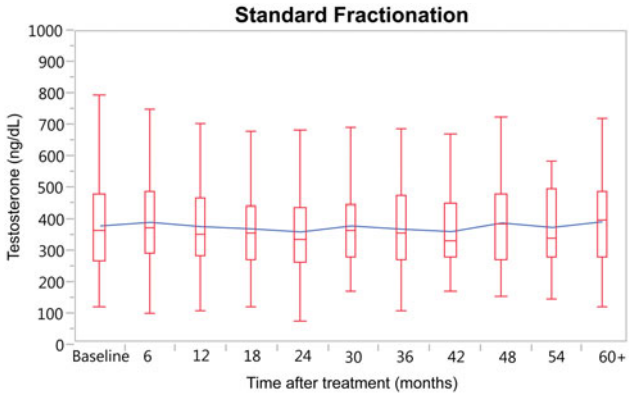

Figure 2. Testosterone concentration across time for patients enrolled on our institution's standard fractionation protocols (PR01 and PR02).

Table 3. Serum testosterone levels for all patients treated with hypofractionation and enrolled in the PR04 protocol.

Month	No. of patients	Median NG/DL	Mean NG/DL	Median Δ	*p* Value
Baseline	204	369	386	N/A	N/A
6	180	360	384	−1%	0.4999
12	167	369	385	2%	0.2850
18	147	370	389	0%	0.3632
24	155	350	378	−2%	0.5069
30	131	379	395	−3%	0.5432
36	103	373	388	−3%	0.3629
42	80	389	389	−4%	0.6594
48	80	375	385	−8%	0.0069
54	49	361	382	−6%	0.4232
60	64	391	406	0%	0.9315

N/A: not applicable.

Discussion

X-ray series

Since prior publications have suggested that Leydig cells are relatively radioresistant (13, 14), the publication by Zagars and Pollack (1), we described earlier did not explicitly state that the 9% decline in ST associated with X-ray-based radiotherapy was due to scatter radiation to the

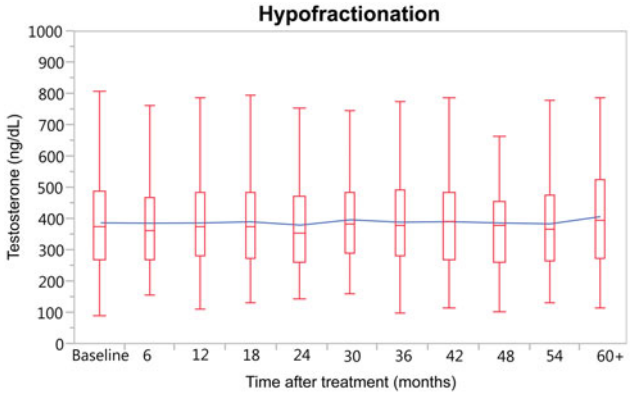

Figure 3. Testosterone concentration across time for patients enrolled on our institution's moderate hypofractionation protocol (PR04).

testicles. The authors' suggestion was that the decline in ST was a response to "stress." Since that publication, seven subsequent studies have demonstrated that X-ray-based radiotherapy is associated with ST suppression. In light of this, the current consensus is that testosterone suppression in this setting is in fact due to scatter radiation dose to the testicular Leydig cells.

In 2001, Daniell et al. (2) published a study comparing ST changes in 33 men who had received post-prostatectomy EBRT and 55 similar men who had undergone radical prostatectomy alone for prostate cancer. No patient had undergone hormonal therapy. At 3–8 years after treatment, irradiated patients experienced a 27% decline in ST compared to the unirradiated men. The authors concluded that the "differences strongly suggested that prominent and permanent testicular damage was sustained during EBRT."

In 2002, Pickles et al. (3) reported on the post-treatment change in ST for 666 men treated with EBRT at 3- to 6-month intervals after treatment. At 6 months, testosterone decreased to an average of 83% of the baseline value.

In 2011, Oerman et al. (4) identified a median 23.75% decline in ST ($p < 0.013$) in 26 patients treated with hypofractionated stereotactic body radiotherapy to a dose of 36.25 Gy in five fractions.

In 2014, Markovina et al. (5) described a statistically significant decrease in ST 6 months after completing intensity-modulated radiotherapy in 51 men. At 1 year after completing radiotherapy, however, there was no significant difference identified and no increase in biochemical hypogonadism.

In 2016, Planas et al. (6) compared ST levels between 92 patients undergoing radical prostatectomy and 28 patients treated with EBRT. At 3 months, ST levels were significantly lower in the irradiated patients ($p = 0.039$). At 12 months, ST levels were also significantly lower ($p = 0.03$).

In 2017, Pompe et al. (7) examined testosterone kinetics after EBRT in 248 assessable patients with a median follow-up of 72 months. The median percentage of decrease to the nadir was 30%. A subgroup analysis of 166 patients treated with intensity-modulated radiotherapy confirmed the results recorded for the entire cohort.

In 2017, researchers (8) published data on ST changes for patients treated with EBRT alone for low- and intermediate-risk prostate cancer on the RTOG 9408 protocol. In this series, radiotherapy was associated with a 9.2% decline in ST at completion of radiotherapy and a median 9.3% decline in ST 3 months after radiotherapy. Both results were statistically significant ($p < 0.001$).

Proton series

In contrast to the series showing declines in ST for patients treated with X-ray-based radiotherapy, in 2011, researchers (9) published the outcomes of 150 patients treated with conventionally fractionated passive-scatter PT for low and intermediate risk prostate cancer on our institution's PR 01 and PR 02 protocols. No change in ST was seen at the end of radiotherapy nor at 6, 12, 18, or 24 months of follow-up.

Similarly, in 2013, Kil et al. (10) showed no change in ST for patients treated with hypofractionated passive-scatter PT on our institution's PR04 protocol at completion of radiotherapy, or 6 and 12 months after treatment.

The current series pools the results for these three protocols with a minimum 5 years of follow-up for all treated patients.

Brachytherapy series

In 2012, Taira et al. (15) described testosterone kinetics after brachytherapy for patients with clinically localized prostate cancer. The authors

observed that patients treated with primary brachytherapy did not experience declines in ST. The authors suggest that the lower scatter dose to the testes with brachytherapy is the likely explanation.

Neutron photon electron scatter

Questions about scatter radiation outside of the beam paths associated with PT were first raised by Hall in 2006 (16). Hall argued that PT would be associated with significant out-of-field radiation scatter due to neutrons produced by the cyclotron. A subsequent analysis by Paganetti et al. (17) found that Hall's calculations were based on measurements performed at the old Harvard cyclotron and that secondary neutron doses could be controlled through the design of the proton beam line.

In 2010, Yoon et al. (18) measured the secondary neutron doses produced by passive-scatter PT using a humanoid phantom. The authors compared these exposures with the secondary photon doses from intensity-modulated radiotherapy for a typical prostate cancer patient. The average secondary dose 20 cm from the isocenter was 0.39 mSv/Gy with protons versus 3.11 mSv/Gy with intensity modulated radiation therapy (IMRT). Based on this nearly 10-fold difference in out-of-field scatter dose with IMRT, the authors estimated that PT in this setting would be associated with a fivefold reduction in the risk of radiation-induced malignancies compared with IMRT.

Hoppe et al. (19) compared semen samples before and after passive-scatter PT in patients treated for localized prostate cancer. At 6–12 months following treatment, men did not demonstrate azoospermia. These results suggest minimal scatter radiation to the testes during treatment, consistent with the measurements made by Yoon et al.

Data loss

While none of the patients in the current series were lost to follow-up, many did not have follow-up testosterone data available. While this data loss is less dramatic for the patients treated on the standard-fractionation trials, which accrued patients from 2006 to 2007, it is notable for the patients treated on the moderate hypofractionation trial which accrued patients from 2008 to 2011. The lack of data in these moderate-hypofractionated patients is attributable to insurance carriers declining to pay for this laboratory study after treatment. This limitation is unrelated to any systemic medical issues which would invalidate the conclusions of the analysis.

Conclusion

While all eight contemporary trials looking at X-ray-based radiotherapy for prostate cancer demonstrate declines in ST, the current series of 358 patients treated with passive-scatter PT showed no such declines with 5 years of follow-up. The lack of testosterone suppression is presumably due to the 10-fold reduction of secondary dose to the Leydig cells – consistent with the data published by Yoon et al. (18). This reduction in secondary dose may ultimately be associated with a lower risk of radiation-induced malignancies, particularly for young patients with substantial life expectancy.

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Declaration of interest

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