ELSEVIER

Urologic Oncology: Seminars and Original Investigations ▮ (2016) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

Original article

Prostate magnetic resonance imaging findings in patients treated for testosterone deficiency while on active surveillance for low-risk prostate cancer

Takeshi Hashimoto, M.D., Ph.D.[a,d], Krishnan Rahul[b], Toshikazu Takeda, M.D., Ph.D.[a], Nicole Benfante, B.S.[a], John P. Mulhall, M.D.[b], Hedvig Hricak, M.D., Ph.D.[c], James A. Eastham, M.D.[a], Hebert Alberto Vargas, M.D.[c,*]

[a] *Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*
[b] *Sexual and Reproductive Medicine Program, Urology Service, Memorial Sloan Kettering Cancer, New York, NY*
[c] *Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY*
[d] *Department of Urology, Tokyo Medical University, Tokyo, Japan*

Received 5 May 2016; received in revised form 30 June 2016; accepted 8 July 2016

Abstract

Objective: To investigate the multiparametric prostate magnetic resonance imaging (mpMRI) findings in patients treated with testosterone replacement therapy (TRT) while on active surveillance for low-risk prostate cancer.

Methods: We retrospectively reviewed 12 patients who underwent mpMRI before and after TRT while on active surveillance. Changes in serum testosterone level, prostate-specific antigen (PSA), prostate biopsy findings, prostate volume, and Prostate Imaging Reporting and Data System Version 2 (PI-RADSv2) score before and after TRT were summarized.

Results: After TRT, there was a significant increase in serum testosterone (516.5 ng/dl vs. 203.0 ng/dl), PSA (4.2 ng/ml vs. 3.3 ng/ml), and prostate volume (55.2 cm^3 vs. 39.4 cm^3). In total, 2 patients had biopsy progression during the study period. The PI-RADSv2 scores before and after TRT were unchanged in 10/12 patients; none of these demonstrated biopsy progression on post-TRT. The PI-RADSv2 scores increased after TRT in 2/12 patients; both showed Gleason score upgrade on follow-up biopsy. Of these 2 patients, 1 patient underwent radical treatment due to clinical progression. The area under the curve for detecting biopsy progression calculated from PI-RADSv2 score after TRT was 0.90, which was better than that calculated from post-TRT PSA level (0.48).

Conclusions: After TRT, mpMRI findings remained stable in patients without biopsy progression, whereas PI-RADSv2 score increase was identified in patients with Gleason score upgrade on follow-up biopsy.

Keywords: Active surveillance; Multiparametric prostate magnetic resonance imaging; Prostate cancer; Testosterone deficiency; Testosterone replacement therapy

1. Introduction

Over the past decade, there has been increasing interest in the detrimental health and quality-of-life effects of testosterone deficiency (TD) in men [1]. Aging men with TD may experience alterations such as depression, fatigue, decreased libido and sexual performance, diminution in muscle volume and strength, and reduction in bone mineral density [2,3]. Increasing age is also associated with increased prevalence of prostate cancer (PCa). At present, most patients with PCa are diagnosed at an early stage and are considered to have a low risk of progression, with active surveillance (AS) gaining wide acceptance as a primary management approach in these patients [4–6].

Although testosterone replacement therapy (TRT) improves the symptoms related to TD, PCa has been considered a relative contraindication to TRT, given prior reports indicating that testosterone induces PCa proliferation and metastasis [7,8]. Despite this, recent studies have

* Corresponding author. Tel.: +1-212-639-3418; fax: +1-212-794-4010.
E-mail address: vargasah@mskcc.org (H.A. Vargas).

http://dx.doi.org/10.1016/j.urolonc.2016.07.004
1078-1439/

suggested that TRT in patients with low-risk PCa while on AS may be safer than conventionally assumed [9–11]. Even if TRT is ultimately proven safe in patients with low-risk PCa on AS, some challenges would need to be addressed regarding the most appropriate approaches for follow-up while on AS to ensure timely detection of cancer progression. The routine use of prostate-specific antigen (PSA) for this purpose could be limited, as it would be difficult to differentiate a rise in PSA because of the physiologic effect of TRT from that related to disease progression [12].

Magnetic resonance imaging (MRI) is being increasingly used in the evaluation of patients with PCa. Previous studies have shown that MRI may be useful to assess AS eligibility and disease progression while on AS [13–17]. However, there are no reports in the literature regarding the effect of TRT on prostate MRI findings of patients with PCa. Thus, the aim of this study was to describe the changes in prostate MRI features after TRT in patients with low-risk PCa undergoing AS, and to evaluate the ability of MRI to detect disease progression in this patient population.

2. Methods

Following institutional review board approval (WA0088–15), we retrospectively reviewed patients' records and extracted patients with PCa managed with AS at our institution. We identified 16 patients who were initiated on TRT during AS between April 2005 and January 2015. Of these 16 patients, 12 patients underwent multiparametric prostate MRI (mpMRI) both before and after TRT and were included in our study. All patients underwent a confirmatory transrectal ultrasound–guided prostate biopsy at our institution to establish eligibility before enrolling in AS. After enrolling our AS program, patients were generally followed at least semiannually with digital rectal examination, PSA measurements, and a review of general health and urinary symptoms. Follow-up biopsy was routinely recommended within 12 to 18 months of starting AS and subsequently repeated every 2 to 3 years or as prompted by a change in digital rectal examination or a sustained PSA increase. All patients were diagnosed with TD based on clinical presentation combined with confirmatory blood test results, specifically serum total testosterone less than 300 ng/dl at consecutive early morning (before 10 AM) measurements. The patients started TRT after a discussion with the treating physician (J.P.M) regarding risks and benefits of TRT. Serum testosterone test was conducted in 4 weeks after TRT initiation, and every 6 months thereafter. The changes in serum PSA and testosterone levels before and after TRT initiation were investigated in each patient.

Given the study length, the imaging acquisition protocol varied slightly in line with the standard of care at our institution at the time the examinations were performed. Of the 24 mpMRIs evaluated (12 before and 12 after TRT), 17 were done with 7 without an endorectal coil for signal reception; 23 mpMRIs included diffusion-weighted images and 18 mpMRIs included dynamic contrast-enhanced sequences. Details of the MRI acquisition parameters are provided in the Supplementary Methods section. For each patient, a fellowship-trained genitourinary radiologist (H.A.V) with 8 years of experience in prostate MRI interpretation evaluated the MRIs performed before and after TRT, and assigned a 1 to 5 suspicion score to each in accordance to the Prostate Imaging Reporting and Data System version 2 (PI-RADSv2) [18,19]. The prostate region with the highest PI-RADSv2 score was considered representative of the overall risk for clinically significant disease on each MRI. All prostate volumes were calculated from multiplanar T2-weighted MRIs using an ellipsoid formula ([transverse × anteroposterior × craniocaudal diameters] / 0.52). We used a Wilcoxon rank-sum test to compare variables before and after TRT initiation. Receiver operating characteristics and corresponding areas under the curve (AUC) were calculated to assess the performance of serum PSA and PI-RADSv2 for detecting disease progression on TRT. A $P < 0.05$ was considered as statistically significant. All analyses were performed using Stata 13.0 (StataCorp, College Station, TX).

3. Results

3.1. Patient characteristics

Patients' characteristics are shown in Table 1. Testosterone gel was dosed in 10 patients, intramuscular injection of testosterone was administered in 1 patient, and subcutaneous testosterone pellets were administered in 1 patient. The median duration of TRT administration was 42.5 months (range: 12–125 mo). In all, 3 patients discontinued TRT after initiation; 1 patient because of PCa progression, 1 patient because of increased hematocrit, and 1 at the patient's request. Serum testosterone levels in 12 patients reached reference range at 6 months after TRT initiation. Median testosterone level of 12 patients was 516.5 ng/dl at 6 months after TRT initiation, which was significantly higher than 203.0 ng/dl just before TRT initiation ($P < 0.001$). The serum PSA level during follow-up periods was shown in Fig. 1. The median PSA level at TRT initiation (baseline), 3 months, 6 months, 12 months, and 24 months ($n = 9$) after TRT initiation were 3.3 ng/ml, 4.2 ng/ml, 4.4 ng/ml, 5.6 ng/ml, and 4.0 ng/ml, respectively (Fig. 1A). The PSA levels at all time points after TRT were significantly higher than the baseline PSA levels ($P < 0.05$). The areas under the curve of serum PSA for detecting disease progression on TRT was 0.48.

3.2. MRI findings and correlation to follow-up biopsies

The baseline mpMRI was performed before the initiation of TRT in all patients. All patients were receiving TRT at