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# Re: Testosterone Therapy in Men with Biochemical Recurrence and Metastatic Prostate Cancer: Initial Observations

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Testosterone replacement therapy (TRT) has been a topic of controversy since its beginnings almost 90 years ago.[1] Initially employed to reverse age-related ailments and as a fountain-of-youth treatment, there was a pendulum shift with the Huggins and Hodges proposal that testosterone activates prostate cancer growth.[2]

In 1981, Fowler and Whitmore reported that 45 of 52 men with metastatic prostate cancer (MET) who received testosterone demonstrated an unfavorable response within 30 days.[3]

The "saturation hypothesis" in 2009 challenged the theory that TRT has such detrimental consequences[4] and allowed many men with treated localized prostate cancer to successfully gain symptomatic relief. However, there are scant published reports on the clinical use of TRT in men with nonlocalized prostate cancer—men with MET, biochemical recurrence (BCR), or prior androgen deprivation treatment. In fact, the 2018 American Urological Association guidelines on TRT makes no recommendation for the use of TRT in hypogonadal men with prostate cancer.[5]

There have been few case reports or series about TRT in patients with "active" prostate cancer.[6] As a recent addition, the aforementioned communication is a retrospective nonrandomized observational study on 22 men with nonlocalized prostate cancer over a 15-year period.[7] Of importance, these men sought relief of their hypogonadal symptoms and were appropriately counseled about the risk of prostate cancer progression and death. The median duration of TRT was 12.5 months (range 2–84). The methods report no mortality in the BCR group and only 7% prostate cancer-specific mortality in the MET group who received TRT. The authors reported appropriate outcome measures that is the standard in studies involving prostate cancer.

However, this report specifically—and the topic—should be approached with caution, given the type and design of the study, the high risk of bias, and the potential negative consequences of such treatment. This is a retrospective analysis of a small cohort, with no preset follow-up protocol that truly details who is experiencing progression, and at what interval after initiation of treatment. There is no control for the type of testosterone and level of replacement. The BCR and MET groups are heterogeneous, including patients with different Gleason grades (6–9), time to BCR, and burden of metastasis. There is no matched control group to, again, truly detect if the observed progression is due to treatment or chance.

Historically, conducting randomized clinical trials on prostate cancer has been challenging due to the need for many subjects followed for a long period of time to detect a difference, but this applies mostly to screening and early treatment. Patients with BCR and MET have more rapid disease progression and shorter survival, hence would not need as many years to detect a difference. This has been recently vindicated with the ability to conduct randomized studies for new drugs used in the treatment of metastatic stage of the disease.[8–10] However, the challenge in this setting will be recruiting enough patients with hypogonadism and advanced prostate cancer for the study to be

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sufficiently powered to detect a meaningful difference. A few strategies have been used to overcome the difficulty in measuring overall and prostate-specific survival; by using surrogates, such as prostate-specific antigen doubling time, radiographic progression, disease progression, and rate of pathological fracture.

Given these limitations, it is likely that the findings of this communication will go unchallenged for many years. As a philosophical choice, some men with active prostate cancer will make the improved quality-of-life decision over the risk of progression and mortality. However, without more concrete evidence, clinicians should be cautioned about the precept that TRT can be used safely in men with advanced BCR and MET prostate cancer. The important findings from the data in this article should lay the groundwork for future controlled research on this important topic.

## Authors' Contributions

A.S. was in charge of data collection and writing initial draft. W.J.G.H. reviewed and revised the draft.

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## Author Disclosure Statement

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### Abbreviations Used

BCR = biochemical recurrence
MET = metastatic prostate cancer
TRT = testosterone replacement therapy