COMMENTARY

Prostate cancer and testosterone: what does the prostate cancer surgeon need to know?

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Prostate cancer and testosterone. When I first started in Urology in the late 1980's, testosterone was considered "bad" as it related to prostate cancer. Many of us were taught the "Fertilizer" analogy where serum testosterone (T) was the fuel or fertilizer that made prostate cancer grow and this was the common patient counseling used for bilateral simple orchiectomy for treatment of advanced prostate cancer. Once we established the Department of Defense Center for Prostate Disease Research (DoD CPDR) database, we decided to look at T levels pre-radical prostatectomy (RP).[1] At that time, it was assumed that a high pre-treatment T level would portend a worse prognosis. To our surprise, low T was independently associated with extracapsular extension (pT3+ disease). At about the same time, Dr. Abraham Morgentaler in Boston was starting to discuss a new concept that he termed the "Saturation Model" suggesting, among other things, that low T may be the real culprit for early progression of prostate cancer.[2] In other words, a prostate cancer that was able to grow in a low T environment has inherent growth advantage. At that time in the early to mid-2000's, this was a radical concept.

Flash forward to 2024. Melao et al in this issue of *The Canadian Journal of Urology* examine T levels pre-RP in 212 patients and show that low T (less than 300) was associated with recurrence and adverse pathology.[3] Furthermore, low T was inversely associated with erectile recovery but not continence recovery. The authors also did a small subset analysis of AR and AR-V7 by T levels and with and without recurrence; however, this sub-study was too small for meaningful conclusions. The overall study is quite small and the cohort seemed to have very favorable disease (only 5% positive margin rate and only 11% recurrence rate at median 40 month follow up) so definitive conclusions cannot be made.

So where does this leave the urologic prostate cancer surgeon in 2024? Ever since our work in 2003, I have tended to obtain a serum T level pre-RP. Certainly,

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from a general men's health screening perspective, I feel it is valuable to know if my surgical patient has preexisting hypogonadism. I do think the knowledge of hypogonadism in RP patients may be important to plan "better" sexual function rehabilitation and early T replacement, but I am not aware of any level I evidence to inform us if this truly improves outcomes. When we do identify hypogonadism preoperatively or in the perioperative period, when is it "safe" to resume or start T replacement in the post-operative period? I am now more comfortable starting T as early as 3 months post op if the PSA is undetectable. However, what if the PSA is detectable? Following up on Dr. Morgentaler's teachings,[2] it may be appropriate to restart or initiate T replacement even with detectable PSA or biochemical recurrence (BCR). In the future, could T level be incorporated into post op nomograms or additive to Decipher or other biomarkers to inform the decision for salvage EBRT with or without androgen deprivation therapy (ADT)?[4] As a specific example for future study, there are actually many RP patients who have a detectable low- level PSA postoperatively who do not always have a recurrence.[5] Does a low, normal or high serum T help us to make clinical decisions for these men as it relates to early salvage radiation versus observation? To my knowledge, this has not been studied but should be.

In summary, the paper by Melao et al[3] supports the concept that a low serum T prior to RP may be an adverse prognostic factor and low T may interfere with erectile recovery, but much more work needs to be done. □

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