

compared to the radiation exposure of a chest x-ray. There are some tests that do not give off any radiation such as an ultrasound or MRI, but most imaging tests give off radiation. Do not be afraid to ask if a certain test is necessary, how much radiation you will be exposed to and whether or not there are other alternatives. For example, calcium scoring using a cardiac CT scan can give off 30 times the dose of radiation of a simple x-ray and may not be needed in some cases because a cholesterol, blood pressure, and weight measurement may provide just as much information without any radiation. However, a dental x-ray and DEXA scan for osteoporosis uses a much lower radiation dose compared to a simple chest x-ray. So, find out the radiation exposure and talk to your doctor.

Y=Yawning

because you are probably tired of reading this Moyad section. There is only one more letter to go, so hang in there my friends and enemies.

Zibotentan

(also known as “ZD4054,” from the company Astra-Zeneca) did NOT work for men with asymptomatic hormone refractory prostate cancer, but there are more study results expected soon! (Reference: Google, as in the search engine that was invented by 2 dudes and one of them is a university of Michigan graduate)

Bottom Line: This is a pill given daily at 10-15 mg, and it is in three PHASE 3 clinical trials right now. It is simple to take and has minimal side effects. Again, it is/was in three phase 3 trials, which is arguably the largest number of phase 3 trials of any other drug in prostate cancer. The first phase 3 trial is comparing this drug against placebo in patients with HRPC and NO clinical metastatic disease (name of the trial is NCT00626548). The second phase 3 trial involves men taking this drug with bone metastasis, but with no to minimal symptoms (name of the trial is NCT00554229) **AND THIS IS WHERE THE DRUG DID NOT WORK IN A RECENT PRESS RELEASE.** However, there is a third phase 3 trial that is attempting to determine if this drug enhances the impact of the chemotherapy drug Taxotere (name of this trial is NCT00617669).

THAT IS ALL FOLKS! LOOK FOR MY NEW PROSTATE CANCER PROMOTING WELLNESS AND NO B.S. BOOKS (for more information or to order

the book call 1-877-722-2264 or 734-913-1640) **THAT WILL BE AVAILABLE SOON!** See you in the spring when we can talk about how the Michigan Football team won their bowl game, and why it is never smart to be an immature pediatrician, piss off an urologist, or let your proctologist act like an ass!

HAPPY HOLIDAYS (politically correct words for whatever the heck you celebrate)!!!

DEBUNKING AN OLD MYTH: TESTOSTERONE REPLACEMENT IS NOT ADDING FUEL TO THE FIRE IN MEN WITH PROSTATE CANCER

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Historically, testosterone supplementation has always been perceived as a taboo subject in men with prostate cancer. It is a fair estimate to say that >99% of physicians in the United States would not consider testosterone replacement for patients who have or had prostate cancer given the concern over prostate cancer progression or recurrence. Why is this? Simply put, we as medical students have been taught during our pre-clerkship that androgen deprivation helps with prostate cancer regression. This is a well-documented fact. At the same time, we also learned from our professors that testosterone administration in patients with prostate cancer would be akin to adding “fuel to the fire” without further discussion. As the decades have passed, it has become apparent that the true relationship between testosterone and prostate cancer has come under heightened scrutiny given the growing numbers of prostate cancer survivors who are symptomatic of hypogonadism.

The historical evidence to first establish the relationship between testosterone and prostate cancer lies with Huggins and Hodges in 1941 when they demonstrated that a reduction in testosterone (by castration or estrogen therapy) caused metastatic prostate cancer to regress [1]. At the same time, they also concluded that the administration of exogenous testosterone resulted in prostate cancer progression. The interesting thing

about this last statement is that it was a conclusion derived from the analysis of a **SINGLE PATIENT**. This individual's PAP level had risen during 18 days of testosterone injections. In retrospect, it appeared that his levels had fluctuated widely before and after testosterone injection and therefore, at best, the results were equivocal.

Through lengthy literature review, it is clear that there is strong evidence to support that by reducing dihydrotestosterone (DHT) levels, one may decrease the development of prostate cancer [2-4]; however, there is **no convincing evidence to demonstrate that giving testosterone truly increases the incidence or recurrence of prostate cancer** [23].

Why is TRT such a hot topic today? If we estimated that 39% of men over the age of 45 are hypogonadal [5] and that the vast majority of men with prostate cancer are over the age of 45, this would add up to a large number of men with hypogonadism after prostate cancer therapy. Additionally, after radical prostatectomy, men are at higher risk of developing depression, erectile dysfunction, and minimal libido. These are similar to symptoms of hypogonadism and these men could definitely achieve clinical improvement from TRT.

Recently, *Shabsigh, et al.* [6] conducted a systematic review of the literature assessing the risk of prostate cancer in men on TRT for hypogonadism. There are 11 placebo-controlled randomized trials, 29 non-placebo-controlled trials of men with no prostate cancer history, and four studies of men with hypogonadism with a history of prostate cancer. None of these studies demonstrated that TRT in men with hypogonadism actually increased the risk of prostate cancer or caused prostate cancer progression. In addition, numerous studies have concluded that there is no significant increase in PSA levels upon administration of testosterone. Some studies have even gone a step further to demonstrate that even supraphysiologic levels have not demonstrated an increase in PSA.

So, if raising a man's testosterone level does not lead to a rise in his PSA, then how does lowering of testosterone to castrate levels cause PSA and prostate cancer regression? This is best explained by the prostate saturation theory which clarifies that prostate tissue growth

is sensitive to changes of serum testosterone only at low levels [7]. This is due to the fact that androgen receptors have a finite capability of binding to androgens [8-9]. As serum testosterone rises, the androgen receptor becomes saturated at which point PSA levels and prostate growth are no longer sensitive to further escalation in testosterone levels. Researchers have confirmed that despite elevations in serum testosterone in men on TRT, the actual level of androgens within the prostate tissue and the androgen-dependent cellular function does not significantly change [10].

To date, there are only three retrospective studies containing 74 patients receiving testosterone after radical prostatectomy. In all of these studies, there was not a single recurrence of measurable PSA. *Kaufman and Graydon* [11] followed seven men with hypogonadism treated with TRT after prostatectomy for 12 years. These patients experienced notable improvement in their symptoms **without any increase in PSA**. *Agarwal and Oefelein* [12] similarly reported on a series of 10 men with hypogonadism treated with TRT after prostatectomy. At 19 months, there were **no increases in PSA associated with increases in testosterone**. *Khera, et al.* [13] also published on 57 patients who suffered hypogonadal symptoms treated with TRT for a median of 13 months **with no increases in PSA**. Lastly, *Sathyamoorthy, et al.* [14] studied 133 patients who had undergone prostatectomy and were treated with TRT. 21 of these patients were classified as high-risk with 8 having Gleason 8 or higher disease, 16 with positive margins, and one with lymph node invasion. **There were no PSA recurrences or statistically significant increases in PSA over the course of treatment**.

Sarosdy, et al. [15] studied 31 men who underwent brachytherapy for prostate cancer. After a median 5 year follow-up after starting TRT after brachytherapy, **not a single patient had stopped TRT due to cancer recurrence**.

Lastly, *Morgantaler, et al.* [16] evaluated the effect of TRT on men with untreated prostate cancer. This was a retrospective study of 14 men who chose watchful waiting for their prostate cancer and who subsequently received TRT for a minimum of six months. All of these men were symptomatic of hypogonadism. PSAs were monitored every three months and follow-up

biopsies were performed annually. Ultimately, the mean duration of TRT after diagnosis was 23.5 months (range 9-43 months). Testosterone levels had changed from <350 ng/dL for all men to an average of 661 ng/dL. **There was no significant change in PSA before and after initiation of TRT.** In addition, there was no change in prostate volume size. Of the 13 men who had follow-up, two patients had evidence of prostate cancer progression. Of these two men, there appeared to be only mild progression of their disease which could have occurred independent of TRT. The 11 remaining men continued on active surveillance and demonstrated no progression of disease after TRT.

All in all, if including abstracts and publications, to date, there have been a total of approximately 292 patients treated with testosterone after prostate cancer therapy and the **risk of recurrence has been estimated at <1%.** An interesting comparison of this statistic can be made if you think that although most patients with prostate cancer who undergo prostatectomy are cured, approximately 15-40% may experience biochemical recurrence [17-18]. The rate of recurrence in this study was <1% which is significantly lower than biochemical failure in a patient with even favorable pathology after prostatectomy.

Is testosterone perhaps beneficial in men with prostate cancer? A study by *Berger, et al.* [19] in Cancer Research demonstrated that the introduction of androgens may in fact have a beneficial effect on prostate cancer by promoting a less aggressive phenotype through androgen receptor expression which converted previously androgen-independent cells into androgen-dependent cells once again.

The contrary has led me to report that there are a plethora of studies which have also clearly documented that low levels of testosterone are more associated with more aggressive prostate cancer. *Hoffmen, et al.* [20] demonstrated that 117 patients diagnosed with prostate cancer with low serum testosterone had an increased percentage of positive prostate cancer biopsies compared to men with normal testosterone levels as well as an increased incidence of Gleason score 8 or higher. *Yamamoto, et al.* [21] has also demonstrated that preoperative serum testosterone levels were in fact an independent and significant predictor of subsequent

PSA recurrence and that after five years, the PSA failure-free survival rate of patients with low preoperative testosterone levels was significantly worse than men with normal serum testosterone.

In May of 2010, Dr. Leibowitz published a case series in which 96 patients were reviewed who had TRT after an initial management for prostate cancer, between 2000 and 2007 [22]. The median age was 61. Most of the men had clinically localized disease and had undergone primary intermittent ADT as initial management after declining surgery or radiotherapy. 12% of the men had metastatic disease at diagnosis. 75% of the men had Gleason 6-7 while 25% had Gleason 8 or higher disease.

The results demonstrated that approximately 40% of the patients on TRT did not have an increasing PSA, but that nearly 60% of men had an increase in PSA leading to cessation of TRT. It is imperative to note that in most patients, biochemical progression on TRT is not synonymous with clinical or symptomatic disease progression. Most importantly, one must understand that in men who still have a prostate gland, it is also a normal response to have PSA progression on TRT due to hyperplasia of normal prostate cells rather than equating PSA progression in these cases as unequivocal disease progression. It would have been helpful to know how many of the 60% of men with PSA progression had prostates still intact to better clarify who truly had disease progression.

After statistical analysis of PSA progression, it was apparent that two factors were associated with a decreased risk of prostate cancer progression. Both having had a prior prostatectomy and being on dutasteride were both associated with a lower risk of prostate cancer progression. On the contrary, a higher baseline PSA at the time of initiating TRT was associated with a greater risk of prostate cancer.

The results speak for themselves! What started off as a theory based on a single patient has been effectively debunked in supporting that TRT is not the scapegoat it was once made out to be!

Here at Compassionate Oncology Medical Group, we have several prostate cancer patients on testosterone replacement who have obtained great clinical benefit of

better energy, strength, potency, libido, memory, concentration, and overall sense of well being which has made a significant impact in improving their overall quality of life.

Resources:

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NEXT TIME...

It has been clearly documented that discordant symptoms, PSA, and bone scan results after treatment have frequently led to therapeutic dilemmas for both the clinician and the patient, in which it is not clear whether to continue or abandon therapy when various indicators are not synchronous. Over the last several years, clinicians and researchers have been attempting to discover a better marker, which may reveal more information on the nature of the disease itself or may be used as a surrogate endpoint to determine a tumor's response to therapy. This has led to the FDA approval of CTC (circulating tumor cell) in 2008. More next time, on the superiority of CTC to PSA and how this test will lead to a more accurate analysis of disease status, prognosis, and better treatment decisions.

NUTRITION CONTROVERSIES

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Foods to Avoid

I do find it amazing that many patients and even cancer physicians do not understand the basics of a healthy diet. While it is true that there are many issues about diet and prostate cancer, these controversies need not keep you from prudent action. The first major point is that men with prostate cancer do not die just from prostate cancer. In men with prostate cancer, the death rate from cardiovascular disease and diabetes is at least equal and may be greater than that from the cancer. The second major point is that it is largely true that the deaths from heart disease and prostate cancer pretty much track each other around the world. Diet and lifestyle patterns associated with a low risk of prostate cancer are also associated with a low risk of heart disease. Finally, we have one clinical trial that shows that a Mediterranean heart-healthy diet actually slows prostate cancer down. So, my basic approach to men with prostate cancer is to advise them to adopt a diet and lifestyle that is also heart-healthy.

Two cuisines stand out as being associated with low risk of disease in general and of prostate cancer and cardiovascular disease. Residents of the Island of Okinawa are the longest lived people on earth. Their diet is rich