Testosterone Therapy in Men With Prostate Cancer: Scientific and Ethical Considerations

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Abbreviations and Acronyms

AR = androgen receptor
DHT = dihydrotestosterone
LH-RH = luteinizing hormone-releasing hormone
PCa = prostate cancer
PSA = prostate specific antigen
RP = radical prostatectomy
RRP = radical retropubic prostatectomy
T = testosterone

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Purpose: Pertinent literature regarding the potential use of testosterone therapy in men with prostate cancer is reviewed and synthesized.

Materials and Methods: A literature search was performed of English language publications on testosterone administration in men with a known history of prostate cancer and investigation of the effects of androgen concentrations on prostate parameters, especially prostate specific antigen.

Results: The prohibition against the use of testosterone therapy in men with a history of prostate cancer is based on a model that assumes the androgen sensitivity of prostate cancer extends throughout the range of testosterone concentrations. Although it is clear that prostate cancer is exquisitely sensitive to changes in serum testosterone at low concentrations, there is considerable evidence that prostate cancer growth becomes androgen indifferent at higher concentrations. The most likely mechanism for this loss of androgen sensitivity at higher testosterone concentrations is the finite capacity of the androgen receptor to bind androgen. This saturation model explains why serum testosterone appears unrelated to prostate cancer risk in the general population and why testosterone administration in men with metastatic prostate cancer causes rapid progression in castrated but not hormonally intact men. Worrisome features of prostate cancer such as high Gleason score, extracapsular disease and biochemical recurrence after surgery have been reported in association with low but not high testosterone. In 6 uncontrolled studies results of testosterone therapy have been reported after radical prostatectomy, external beam radiation therapy or brachytherapy. In a total of 111 men 2 (1.8%) biochemical recurrences were observed. Anecdotal evidence suggests that testosterone therapy does not necessarily cause increased prostate specific antigen even in men with untreated prostate cancer.

Conclusions: Although no controlled studies have been performed to date to document the safety of testosterone therapy in men with prostate cancer, the limited available evidence suggests that such treatment may not pose an undue risk of prostate cancer recurrence or progression.

Key Words: testosterone, prostatic neoplasms, hypogonadism, androgens

THE use of T therapy in men with PCa is controversial.[1,2] Although there has been a long-standing consensus that T therapy is contraindicated in these men due to the potential for androgenic stimulation causing PCa recurrence or progression, recent evidence suggests that such treatment may not be as risky as once assumed.[3] Indeed several small case series have reported no biochemical recurrence in men following radical

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prostatectomy[4,5] or brachytherapy,[6] and a recent case report noted a decrease in PSA in a man with untreated PCa who received T therapy for 2 years.[7]

The impetus for reconsidering T therapy in men with PCa stems from several factors, one of which is the increasing recognition of the health benefits of T therapy in hypogonadal men, including improvements in energy, vitality, sexual desire, erectile function, body composition and bone mineral density.[8,9] Another impetus is failure to observe a significant increase in PCa associated with T therapy in the general population, as would be predicted by the traditional androgen dependent model of PCa.[1] Finally, there has been pressure from the substantial number of PCa survivors who desire an improved quality of life.

Remarkably no modern controlled studies have investigated the effects of T therapy in men with PCa.[10] This lack of evidence creates a dilemma for the clinician faced with a symptomatic hypogonadal man with a history of PCa. On the one hand, is it reasonable to offer T therapy when tradition and training argue that treatment poses a substantial risk of more rapid PCa growth? On the other hand, is it ethical to deny a beneficial treatment when the risk is theoretical but unproven?

Despite the absence of controlled trials, there is a wealth of scientific and clinical studies regarding the relationship of androgens and PCa that are relevant to this issue. These data are reviewed and synthesized to determine the relative merits of T therapy in men with a history of PCa.

ORIGIN OF THE PROHIBITION AGAINST TESTERONE THERAPY IN MEN WITH PROSTATE CANCER

The original concept that PCa is androgen dependent arose from the work of Huggins and Hodges in 1941, who reported that castration in men with metastatic PCa caused a rapid decrease in the serum marker acid phosphatase and T administration caused an increase in acid phosphatase.[11] In 1967 Prout and Brewer reported that several weeks of T administration resulted in PCa progression or death in 5 of 10 men with recurrent disease after castration.[12] In 1981 Fowler and Whitmore reported that T administration caused an "unfavorable response" in 45 of 52 men with metastatic PCa, most within 30 days.[13] These early observations led to the belief that higher serum T causes more rapid PCa growth and the general consensus that T administration is contraindicated in men with PCa.

CURRENT STATUS OF TESTOSTERONE THERAPY IN MEN WITH PROSTATE CANCER

The androgen dependent model of PCa growth has been reinforced in the modern era by several observations.[10] Androgen deprivation therapy causes reliable and often dramatic decreases in PSA, discontinuation of LH-RH agonist therapy with intermittent therapy causes a several-fold increase in PSA in parallel with increasing serum T and the transient increase in serum T seen with LH-RH agonist therapy, called T flare, has been associated with negative PCa outcomes.[14] These observations have supported ongoing recommendations against T therapy in men with PCa. The Endocrine Society Clinical Guidelines state, "We recommend against starting testosterone therapy in men with breast or prostate cancer," although the low quality of evidence supporting this recommendation was noted.[9] The United States Food and Drug Administration has required manufacturers of T products to include statements in product inserts that androgens are contraindicated in men with known or suspected PCa, without documentation or evidence. No policy statements or clinical guidelines have been published by the American Urological Association regarding T therapy in men with a history of PCa.

Until fairly recently there was little reason to question the traditional prohibition against T therapy in men with PCa or the underlying belief that serum T was a primary driver of PCa growth throughout the range of T concentrations, since T therapy was infrequently prescribed and its benefits were not widely appreciated.[10] However, the increased interest in T therapy during the last 10 to 15 years has sparked a reexamination of the evidence regarding T and PCa, calling into question the traditional view that higher serum T necessarily causes more rapid PCa growth.[3] Thus, a review by the United States Institute of Medicine in 2004 concluded, "In summary, the influence of testosterone on prostate carcinogenesis and other prostate outcomes remains poorly defined. . . ."[15] In addition, a review on the risks of T therapy noted there was "no compelling evidence" that exogenous T increased the risk of PCa.[16]

MECHANISM OF ACTION OF ANDROGENS ON PROSTATE TISSUE

There is no dispute that androgens have an important role in the development and growth of prostate tissue. The mechanism of action of androgens on prostate tissue has been recently reviewed.[17] Briefly T enters the prostate cell where it is largely metabolized in the cytoplasm to DHT by the enzyme 5α-reductase. DHT is the primary

intraprostatic androgen, as it binds more avidly than T to the AR, which in turn is responsible for mediating androgenic action on the prostate cell. Once bound the androgen-AR complex translocates to the cell nucleus where it is able to bind directly to DNA, thus exerting its proliferative and trophic effects.[17]

A key observation is that AR has a finite binding capacity for androgen.[18] Maximal binding (saturation) in the human, dog and rat prostate has been demonstrated to occur at low androgen concentrations of 2 to 3 nM (approximately 60 to 90 ng/dl).[19,20] Once AR is saturated with androgen, higher androgen concentrations do not result in greater androgen-AR binding (fig 1).

ANDROGEN EFFECTS ON PROSTATE GROWTH IN ANIMAL STUDIES AND CANCER CELL LINES

Multiple studies in animal systems demonstrate a steep dose response curve for prostate growth with respect to androgen concentrations.[18] However, as androgen concentrations increase, a plateau is reached and further increases in androgen concentration produce little or no additional growth.[18] Similar results have been obtained for the androgen sensitive LnCaP prostate cancer cell line, with even log increases in DHT or T resulting in no greater growth rate after a plateau is reached.[21,22] Thus, prostate growth becomes androgen indifferent at higher concentrations. These results indicate a limit to the ability of androgens to stimulate prostate tissue growth (fig 2).[18]

ANDROGEN DEPRIVATION IN MEN WITH PROSTATE CANCER

Substantial, rapid decreases in PSA are seen with androgen deprivation in men with advanced PCa. Kuhn et al randomized 36 men with disseminated PCa to the LH-RH agonist buserelin with or without an anti-androgen.[23] In both groups mean PSA was greater than 500 ng/ml at baseline and had decreased by more than 70% by day 29. A study of the LH-RH antagonist abarelix in men with stage D PCa revealed a 90% decrease in PSA.[24]

ANDROGEN DEPRIVATION IN MEN WITH NORMAL PROSTATE

In 7 men treated with the LH-RH agonist nafarelin for 6 months followed by a 6-month recovery period serum T decreased from a mean of 435 ng/dl to less than 50 ng/dl, followed by recovery to 482 ng/dl at 12 months.[25] PSA decreased from a baseline mean of 2.95 ng/ml to a nadir of 0.5 ng/ml at 6 months, followed by recovery to 2.98 ng/ml. PSA correlated significantly with T concentration during treatment and followup. Prostate volume decreased from 50 to 37 cc at 6 months, followed by recovery to 47 cc at 12 months. The increase in PSA from T deficient to T replete represented an increase of approximately 600%.

Another form of androgen deprivation is provided by the 5α-reductase inhibitors finasteride and dutasteride, which severely reduce intracellular concentrations of DHT. Treatment results in a median PSA decrease of approximately 50% by 3 to 12 months and a decrease in prostate volume by

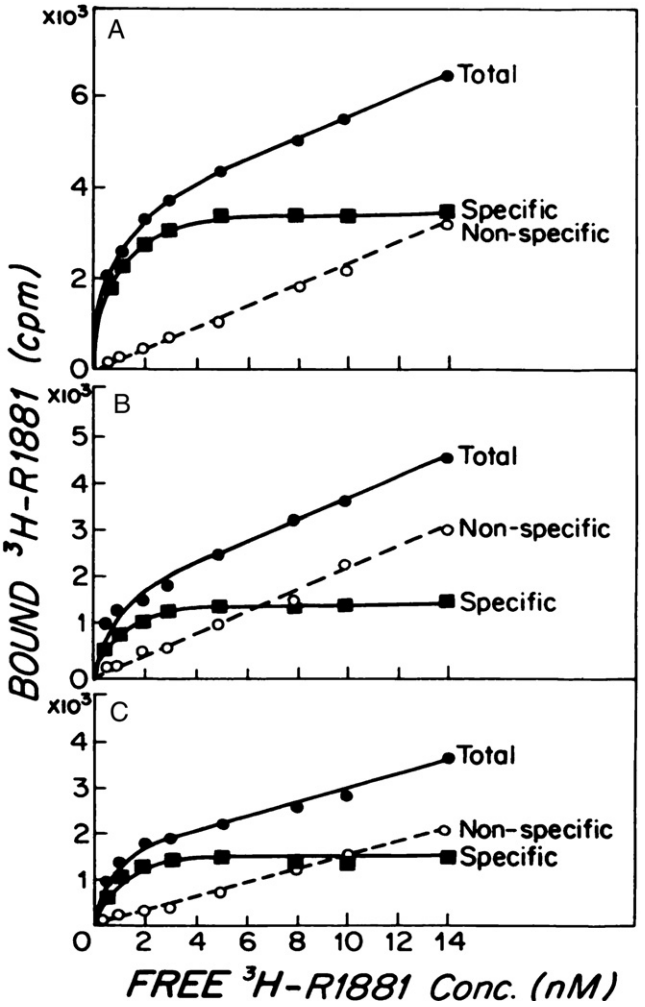

Figure 1. Binding of synthetic androgen [3H]R1881 to androgen receptor in Noble rat ventral (*A*), dorsolateral (*B*) and anterior (*C*) prostate. Note that specific androgen binding to AR reaches maximum at low androgen concentrations (2 to 3 nM, roughly 60 to 90 ng/dl) in all 3 prostate lobes without further binding over wide range of increasing concentrations of [3H]R1881. Choice of [3H]R1881 as ligand for AR binding assay is due to its high affinity for AR and low affinity for nonspecific plasma proteins, including sex hormone binding globulin. *Conc.*, concentration. Reprinted with permission.[20]

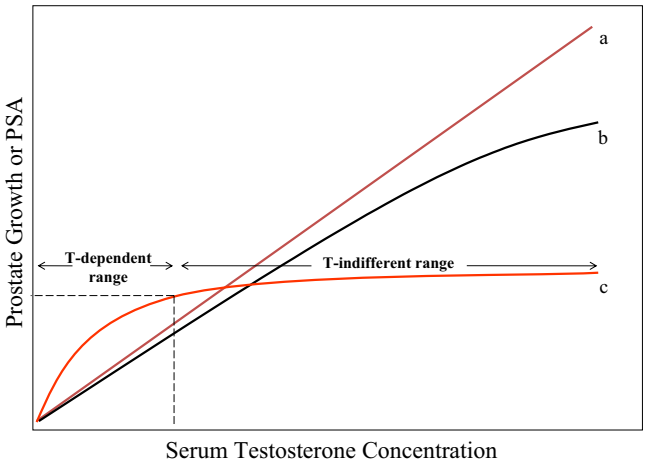

Figure 2. Saturation of prostate growth with regard to testosterone. Traditional androgen dependent view of prostate assumed growth would increase as serum T concentrations increased (curves *a* and *b*). Current evidence suggests that prostate growth and its surrogate, PSA, are sensitive to changes in serum T at low extreme of T concentrations (androgen sensitive) and reach growth plateau as serum T increases. Once this growth plateau is reached, presumably due to maximal binding of androgen to AR, system is considered saturated and no further prostate growth occurs even with large increases in T (androgen indifferent) (curve *c*).

a third.[26] Discontinuation of treatment results in restoration of baseline PSA, representing a doubling from the DHT deprived state. These results demonstrate that creation or resolution of androgen deprivation causes large PSA changes in benign and malignant prostate tissue.

IMPACT OF SERUM TESTOSTERONE ON PSA AND PROSTATE VOLUME IN THE GENERAL POPULATION

In contrast to the large PSA changes seen with T variation in men on androgen deprivation, naturally occurring variation in serum T appears to have little influence on PSA. Monath et al investigated the relationship of endogenous T concentration on PSA in 150 men without prostate cancer.[27] Mean age was 60.1 years (range 41 to 79) and 96% of the men had T concentrations within the normal range. No correlation was found between T and PSA. A much larger sample (1,576 men) from the Massachusetts Male Aging Study also revealed no correlation between PSA and T concentrations.[28]

In several studies the effect of increasing T into the supraphysiological range has been investigated. Cooper et al randomized 31 healthy men with an average age of 28 years to weekly T injections of 100, 250 or 500 mg.[29] Supraphysiological T concentrations of 1,138 and 1,994 ng/dl were noted for the 250 and 500 mg groups, respectively. No significant changes in PSA or prostate volume were noted in any group during the 40-week study period. Bhasin et al administered 600 mg T or placebo weekly for 10 weeks to men ranging in age from 19 to 40 years.[30] Mean PSA did not change significantly from baseline despite T concentrations greater than 2,800 ng/dl in the T treated group.

TESTOSTERONE THERAPY IN HYPOGONADAL MEN

Steidle et al studied T therapy in 406 hypogonadal men randomized to 90 days of treatment with placebo, 1 of 2 doses of T gel or a T patch.[31] End of study PSA in T treated men did not differ significantly from that in men treated with placebo. In addition, a meta-analysis of 19 controlled T therapy studies revealed no greater proportion of adverse prostate outcomes, such as increased PSA or PCa development, in men treated with T vs placebo.[32]

Individual PSA responses to T therapy in hypogonadal men vary considerably. In a study of 58 men who underwent 12 months of T therapy mean PSA increased 17% over baseline. However, 43% of the group did not demonstrate any PSA increase, including 20% in whom PSA decreased.[33]

RELATIONSHIP OF SERUM T TO PCa

At least 21 longitudinal studies have examined the relationship of serum sex hormones to PCa development, and a majority revealed no significant relationship between androgens and PCa.[1,3] A small number revealed isolated associations with some androgen measure, such as the Baltimore Longitudinal Study of Aging in which a statistically significant association was noted between PCa and increasing quartiles of calculated free T, although mean calculated free T was numerically lower in the PCa group than in men without PCa.[34] In 2008 a global collaborative study was performed to investigate this issue with greater statistical power obtained by pooling original data from 18 individual studies, including the Baltimore Longitudinal Study of Aging.[35] These pooled data included 3,886 men with PCa and 6,438 without PCa. The results revealed no association between any serum androgen measurement and PCa, including total and free T. Specifically men with PCa did not have higher serum concentrations of T or other androgens than men without PCa and men with high serum T were not at any greater risk for PCa than men with low serum T. The primary conclusion of this major study was that variations in serum T within the naturally occurring range have no impact on PCa.[35]

Additional studies have investigated the relationship of serum T to PCa features or outcomes. These

studies have uniformly shown no relationship to high T or an association of worrisome features with low T, including high Gleason grade, worse stage at presentation, risk of positive surgical margins and worse survival.[36] Yamamato et al investigated the risk of biochemical recurrence after RP in 272 men, including 49 with serum T in the hypogonadal range (less than 300 ng/dl).[37] The risk of PSA failure at 5 years was 2.7-fold higher for men with low T than that for men with normal serum T.

TESTOSTERONE THERAPY IN MEN WITH A HISTORY OF PROSTATE CANCER

There have been 3 small case series on results of T therapy after treatment for localized PCa. Kaufman and Graydon reported the results of T therapy after RP in 7 men with undetectable PSA.[4] No recurrences were noted with followup as long as 12 years. Agarwal and Oefelein reported no biochemical recurrences after RP in 10 men with undetectable PSA.[5] Sarosdy reported on T therapy in 31 men who had undergone brachytherapy.[6] At a median followup of 4.5 years PSA was less than 1.0 ng/ml in 100% of the men and less than 0.1 ng/ml in 74%. Three additional series revealed no recurrence after RRP in 21 men,[38] a single biochemical recurrence after RRP 12 months after T initiation in a man with Gleason score 8[39] and a single recurrence in 20 men treated with RRP or external beam radiation.[40] Altogether biochemical recurrence was noted in 2 of 111 men (1.8%) who received T therapy after various forms of localized PCa therapy.

In an unpublished study from the University of Washington whether weekly T injections for 1 month could unmask residual PCa in men deemed to be at high risk for recurrence following RP was investigated. None had an acute increase in PSA, although several men subsequently had recurrent disease (Lange, personal communication). A recently published case report detailed a decrease in PSA after 2 years of T therapy in an 84-year-old hypogonadal man with untreated PCa.[7]

Several studies from the pre-PSA era investigated T administration in men with advanced or metastatic PCa. Huggins and Hodges reported acid phosphatase results of T administration in 2 men with metastatic PCa.[11] Acid phosphatase increased in a castrated man, whereas results were equivocal in a noncastrated man. Prout and Brewer compared T administration in 2 groups of men with advanced PCa.[12] Of 10 men with recurrent disease after castration 5 had progression or died within several weeks. In contrast, no clinical progression or increase in acid phosphatase was noted in a second group of 26 men consisting of 20 who were intact and 6 who had undergone recent castration. The authors noted that several of these men exhibited benefits from T administration, including improved sense of well-being, increased appetite and decreased bone pain.[12]

Although Fowler and Whitmore reported that 45 of 52 men who received T administration demonstrated an "unfavorable response," all but 4 of these men had undergone androgen deprivation.[13] The authors noted a relatively benign response to T administration in the 4 untreated men, of whom 3 continued to receive daily T injections for 52, 55 and 310 days, respectively. They speculated that naturally occurring T concentrations were sufficient to produce near maximal PCa stimulation.[13]

The concept that naturally occurring T concentrations may already provide maximal PCa stimulation is supported by the observation that T flare did not produce an increase in PSA in 2 studies of LH-RH agonists in men with metastatic PCa.[23,24] Mean PSA was greater than 500 ng/ml in 1 study, indicating a substantial metastatic burden.[23] A small (18 men) study from Japan revealed an increase in PSA during T flare. However, the study included several men older than 80 years, raising the possibility that some individuals may have been substantially androgen deficient at baseline.[41]

DISCUSSION

Overall the evidence fails to support the long-standing assumption that higher T leads to greater PCa growth throughout the entire range of T concentrations. Although it is clear that PCa is exquisitely sensitive to variation in serum T within the near castrate range, studies in animal models and PCa cell lines demonstrate that there is a limit to the ability of androgens to stimulate prostate growth.[20–22] Once maximal growth has been achieved, even log increases in androgen concentration produce no additional growth. In healthy men increasing T well into the supraphysiological range causes no increase in PSA or prostate volume.[29,30] Contrary to what one would expect if PCa growth rates were influenced by serum T concentration, there appears to be no association between high serum T and risk of clinical PCa.[35] In men with known PCa worrisome prognostic features have been associated with low rather than high T,[36] including evidence that PCa risk is associated with the severity of T deficiency.[42]

Thus, the evidence indicates that PCa growth behaves in an androgen dependent manner at low T concentrations and becomes androgen indifferent at higher concentrations. A saturation model has been proposed to describe this relationship of T and PCa,[1,18] based primarily on the finite capacity of AR to bind androgen.[19,20] An additional mechanism is suggested by Marks et al, who found no increase in intraprostatic

concentrations of T or DHT, or changes in cellular markers of proliferation after 6 months of T therapy in hypogonadal men, despite large increases in serum T.[43] This finding suggests that the hormonal milieu in the prostate is somehow protected from large changes in serum T. Although it is unknown at what serum T concentration PCa develops reduced sensitivity to androgenic stimulation, this value appears to be low, considering the minimal change in PSA noted with T therapy in hypogonadal men.[18]

To date 6 studies have provided information on a total of 111 men treated with RP, brachytherapy or external beam radiation therapy.[4–6,38–40] Biochemical recurrence was noted in 1.8% (2 men), a recurrence rate no higher than published series in favorable groups.[44] The absence of recurrence in 31 men treated with brachytherapy provides some reassurance that T therapy may not present undue risk even when the prostate remains in situ.[6] There are no data to indicate that a delay in initiation of T therapy impacts outcome. Caution must be exercised in drawing conclusions from this limited clinical experience of T therapy after treatment of PCa.

A more general question is whether T therapy may be considered even when there is no certainty that PCa has been eradicated, such as in men undergoing surveillance or those with persistent symptoms of T deficiency long after discontinuation of LH-RH agonists. This possibility is supported by a report of PSA decrease in a man with untreated PCa who received T therapy for 2 years,[7] as well as by historical studies revealing that T administration was associated with a benign clinical course in noncastrated men with metastatic disease.[12,13] In addition, T therapy in men at high risk for PCa based on a history of high grade prostatic intraepithelial neoplasia revealed little indication of increased risk.[45]

Clearly no solid recommendations are possible until data are available from randomized controlled trials. However, it seems logical to surmise that many men with untreated, albeit undiagnosed PCa must already be receiving T therapy since 1 in 7 (15%) hypogonadal men with PSA less than 4.0 ng/ml has biopsy detectable PCa.[42,46] If increasing T in hypogonadal men causes more rapid PCa growth, one would predict a substantial rate of new PCa cases detected in T trials. However, a meta-analysis revealed that T treated men were at no greater risk for negative prostate outcomes (increased PSA, PCa rates) than placebo treated men.[32] A large clinical trial would best be able to assess degree of risk from T therapy but it is important to recognize the possibility that such a study may demonstrate a beneficial impact of T therapy on PCa outcomes based on the association of worrisome PCa features with low serum T[36] as well as experimental evidence that androgens may inhibit prostate proliferation and promote a more differentiated, less invasive phenotype.[47]

Not all studies are consistent with the saturation model of PCa growth. Svatek et al reported that intramuscular injection of 400 mg T was associated with a greater increase in PSA at 4 weeks in men with vs without PCa,[48] and others have published anecdotal development of PCa after initiation of T therapy.[49] These results underscore the possibility that individuals may vary in susceptibility to androgenic stimulation of PCa. In particular, men with severe T deficiency, especially those with advanced disease treated with androgen deprivation, would be expected to be at high risk for PCa progression or recurrence with T therapy since these men are likely to have substantial unmet capacity for additional androgen stimulated PCa growth.[18] Although the reduced PCa rate in finasteride treated men vs placebo treated men in the Prostate Cancer Prevention Trial would appear to support the traditional concept that higher androgens increase PCa risk,[50] it is worth noting that in that study relative androgen deprivation of the prostate due to finasteride was investigated but whether increasing androgens in an androgen replete prostate would influence PCa risk was not.

In the end clinicians must make their own determination regarding the relative merits of T therapy for men with a history of PCa, considering individual circumstances, patient desires and the rapidly changing assessment of risk in this situation. Whereas most clinicians are familiar with the ethical concept “Primum non nocere,” or “First, do no harm,” all medical treatments entail some degree of risk, as does withholding treatment. A lesser known, but arguably more appropriate dictum for medical care is “Salus aegroti suprema lex,” or “Do what is best for the patient,” a concept that incorporates clinical judgment amid uncertainty, and honors the wishes and goals of the patient.

Although the safety of T therapy in men with PCa has not been established, it is also true that the traditional assumption of more rapid PCa growth with higher T has failed to find compelling scientific support, except for the special case of pharmacological or surgical androgen deprivation. It is worth considering that a normal serum T concentration is not currently regarded as a risk factor for recurrence in a man who has been successfully treated for PCa. Why then should it matter if this normal T concentration occurs naturally or by pharmacological assistance? Until more definitive data are available, clinicians who wish to offer the benefits of T therapy to their hypogonadal patients may find it prudent to inform these men that the risk of PCa progression or recurrence is unknown and to document informed consent before proceeding with treatment.

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