Testosterone therapy in men with prostate cancer: literature review, clinical experience, and recommendations

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For several decades any diagnosis of prostate cancer (PCa) has been considered an absolute contraindication to the use of testosterone (T) therapy in men. Yet this prohibition against T therapy has undergone recent re-examination with refinement of our understanding of the biology of androgens and PCa, and increased appreciation of the benefits of T therapy. A reassuringly low rate of negative outcomes has been reported with T therapy after radical prostatectomy (RP), radiation treatments, and in men on active surveillance. Although the number of these published reports are few and the total number of treated men is low, these experiences do provide a basis for consideration of T therapy in selected men with PCa. For clinicians considering offering this treatment, we recommend first selecting patients with low grade cancers and undetectable prostate-specific antigen following RP. Further research is required to define the safety of T therapy in men with PCa. However, many patients symptomatic from T deficiency are willing to accept the potential risk of PCa progression or recurrence in return for the opportunity to live a fuller and happier life with T therapy.

Keywords: androgen deprivation; androgens; hypogonadism; prostate cancer; prostate-specific antigen; testosterone; testosterone therapy

INTRODUCTION

Over the last several years, there has been a dramatic global surge in testosterone (T) prescriptions. This rise in treatment has been spurred by greater awareness of the positive impact of T deficiency on health and well-being, coupled with a reduced concern regarding T therapy and prostate cancer (PCa) risk. For several decades, it was assumed that higher serum levels of T would increase the risk of developing de novo PCa or cause rapid growth of an occult PCa. Indeed, the fear of PCa has been the greatest international concern regarding T therapy. Major changes in our understanding of the relationship of PCa to androgens as well as new, reassuring evidence has brought the traditional view of the relationship of T and PCa into question. This new understanding has lowered the threshold for clinicians to consider T therapy in symptomatic men, including those with a prior history of PCa, a practice that has been contraindicated for decades.

T deficiency is common and underdiagnosed. It has been estimated to affect 2.1%–12.8% of middle-aged to older men in the US and Europe. The numbers of affected men is likely to grow as the population ages in many countries. For example, in the US, the fraction of the population over 65 is growing at a rate 2–3 times of that compared to younger men.

T therapy has been shown to offer a number of important benefits for sexual and nonsexual symptoms, as well as improvement in metabolic parameters such as increased lean mass, decreased fat mass, reduced insulin sensitivity, and improved bone mineral density. In assessing these benefits against potential risks, it is critical to consider the relationship of T and PCa. Not only has our understanding of this relationship changed dramatically, but some centers, including ours, now even offer T therapy to selected men with a history of PCa. The purpose of this article is to review the historical and current literature to provide a modern perspective on the use of T therapy in men with a history of PCa.

METHODS

A MEDLINE search was conducted from 1940 to 2014. The keywords androgen, T, prostate, and PCa were employed. Articles germane to this review were selected for discussion. Clinical comments have been added based on research experience in the field spanning more than 25 years, and clinical experience with T therapy in more than 200 men with a history of PCa.

RESULTS

Historical studies

In 1941 Huggins and Hodges reported that men with metastatic PCa demonstrated a decline in the serum marker acid phosphatase with castration or estrogen administration. Both treatments markedly reduced serum T. These authors also reported that administration of T injections over 2 weeks resulted in an increase in acid phosphatase. Fowler and Whitmore reported unfavorable outcomes in 45 of 52 men with metastatic PCa treated with T, most occurring within 30 days. These experiences led to the concept that T “activated” PCa, and...
that offering T therapy to men with existing PCa was like “pouring gasoline on a fire,” a concept taught to generations of medical students around the world.

Yet these historical reports and others already contained information that should have led to a more nuanced view. Huggins and Hodges only provided information on one hormonally intact individual who received T injections, with erratic, uninterpretable acid phosphatase results.10 This fact had been overlooked until noted upon re-review of the article in 2006.7 All but four of the men in the study by Fowler and Whitmore were already androgen deprived when they received T injections.12 11 Among four hormonally intact men, no rapid progression or other unfavorable outcomes were reported for three of these men, one of whom received T injections for nearly a year.2 Prout and Brewer reported rapid progression or death in approximately 50% of men who had been previously castrated when given exogenous T.12 However, hormonally intact men that received T treatment did not demonstrate these negative outcomes.

These experiences strongly suggested that T therapy did indeed cause rapid progression in androgen-deprived men, but not in men with naturally occurring serum T concentrations.2 This critical distinction contributed to development of the Saturation Model, described below.13,14

**Saturation model**

The saturation model has altered conceptual thoughts regarding the relationship between androgens and PCa. Whereas it had been assumed for decades that increasing serum androgen concentrations would increase PCa growth, it is now appreciated that PCa is exquisitely sensitive to changes in serum androgens at very low concentrations, yet behaves in indifferent fashion with changes in concentration above a saturation point, the concentration of maximal androgen stimulation.15,14 In other words, there is a limit to the ability of androgens to stimulate prostate growth, whether benign or malignant. This explains why serum prostate-specific antigen (PSA) does not correlate with serum T concentrations in a normal population,15 yet PSA declines dramatically with experimental androgen deprivation in healthy volunteers,16 and why 5 alpha reductase inhibitors that produce castrate-level dihydrotestosterone (DHT) concentrations reduce serum PSA by approximately half.17 Yet administration of supraphysiological T doses to healthy volunteers for as long as 9 months does not result in increased PSA or prostate volume.15 Men with high serum T concentrations appear at no greater risk of developing PCa, or aggressive PCa, compared with men with relatively low serum T concentrations.6,19

Although it has been argued that the saturation model is theoretical and unproven,20 this is a misunderstanding of how the saturation model was developed, and its purpose. The traditional concept taught to generations of medical students and trainees had been that PCa is androgen-dependent in the sense that ever-increasing serum androgen concentrations lead to ever-increasing PCa growth. This concept, unchallenged for nearly 70 years, is contradicted by considerable evidence, as noted above.2,5,14 The saturation model was therefore developed to account for, and to unify, the known disparate observations regarding the relationship of androgens to the prostate, benign and malignant, in humans, animals, and in *in vitro*.14 The value of the saturation model is that it provides a logical framework for understanding why prostate tissue behaves in an androgen-dependent manner in some cases and in an androgen-insensitive manner in others. A simple, yet elegant relationship was found to apply based on androgen concentration. Similar relationships are found throughout biology. The saturation model is thus not an unproven theory, but rather an accurate description of how PCa behaves with regard to androgens. The power of such a model is that it may then predict how PCa will behave in less explored situations, such as the use of T therapy in men with PCa.

Evidence from experimental and observational studies, as well as clinical experience, indicates the saturation point, that is, the concentration at which androgen-driven stimulation of prostate tissue reaches a maximum, is approximately 250 ng dl⁻¹ (8 nmol l⁻¹).21–23 This value falls within the mild to moderate hypogonadal range. Practically, this means that men with serum T lower than this value will have falsely depressed serum PSA concentrations, which will increase with normalization of serum T, as with T therapy. This initial increase generally reaches a maximum by 3–4 months. The theoretical saturation curve (Figure 1) first proposed in 200722 is nicely confirmed by real-life baseline serum PSA values in 2967 men presenting to an andrology clinic, demonstrating that increasing severity of serum T deficiency below the saturation point of 8 nmol l⁻¹ (approximately 250 ng dl⁻¹) is associated with more severe reductions in serum PSA, whereas mean serum PSA is unchanged throughout the range of serum T concentrations above the saturation point (Figure 2).22

A number of mechanisms may underlie the saturation model. One is that maximal binding of androgen to the androgen receptor in human prostate tissue is achieved *in vitro* at approximately 4 nmol l⁻¹.24 This value is consistent with the observed saturation point of approximately 8 nmol l⁻¹ in the clinical setting.21–23 with the disparity explained by the presence of sex hormone binding globulin *in vivo*, which tightly binds approximately half or more of circulating T. A second mechanism is that intra-prostatic androgen concentrations appear to be somewhat independent of serum concentrations. Marks et al. demonstrated that 6 months of T injections in T-deficient men substantially elevated serum T concentrations but failed to increase prostate tissue concentrations of T or DHT.25 Other mechanisms may also be operative. The take-home messages are: the prostate is indeed dependent on androgens for optimal growth; there is a limited ability of androgens to stimulate prostate growth; and maximal androgen-driven growth is achieved at relatively low serum T concentrations.

The saturation model impels a change in the traditional teaching that T is “like food for a hungry tumor.” Rather, it suggests that T is “like water for a thirsty tumor.” The critical distinction is that once thirst is quenched, additional water serves only as excess.

**Figure 1:** Proposed saturation model for the relationship of prostate cancer (PCa) growth and serum T concentration. The traditional belief has been that higher T concentration caused increasing rates of PCa growth, as represented by curves a and b. All available evidence demonstrates a powerful effect of T on PCa growth at low T concentration, yet little or no effect above the near-castrate range. The proposed model for the relationship between T and PCa is thus shown as curve c and is consistent with a saturation model, as seen in many other biologic systems. From Morgentaler.14

![Proposed saturation model](image-url)
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Figure 2: Saturation curve of serum prostate-specific antigen (PSA) and serum testosterone. From Rastrelli et al.22

There are several important implications and predictions of the saturation model:
1. Reducing serum T concentrations below the saturation point (approximately 250 ng dL⁻¹) will reduce serum PSA and cause reduction in prostate volume for men with benign or malignant prostate tissue
2. Raising serum T in men with levels anywhere below the saturation point will result in a rise in PSA and tissue growth
3. Androgen-driven growth is maximal at the saturation point. Increases in serum T above this level result in limited or no additional growth
4. Men with serum T far below the saturation point will demonstrate greater increases in PSA with T therapy than men with serum T concentrations slightly below the saturation point.

Current use of testosterone therapy in men with prostate cancer
The use of T therapy in men with PCa has been contraindicated for several decades, based on experiences in the 1980s and earlier that suggested that raising T in a man with PCa was like “feeding a hungry tumor” (see above), or “pouring gasoline on a fire.” In 1981, Fowler and Whitmore reported the Memorial Sloan-Kettering Cancer Center’s experience with administration of T injections in men with metastatic PCa.11 They found that 45 of 52 men demonstrated an “unfavorable response” with T injections, most within 30 days. The logic of avoiding T therapy in men with PCa seemed supported by the everyday clinical experience of PCa specialists, in whom the goal of therapy for men with advanced disease has been to deprive them of as much androgen as possible.

However, it was not widely appreciated that in the series by Fowler and Whitmore, all but four of the men were already androgen-deprived, and of the four intact men who received T injections, three did well, receiving daily treatments for 52, 55, and 310 days.2 Prout and Brewer noted that men who received injections often experienced improved sense of well-being,12 and their data showed that among men that received T injections, those that had been previously androgen-deprived progressed rapidly, whereas intact men or those that had very recently undergone castration had a benign cancer response to T injections.12

With growing appreciation of the negative clinical impact of T deficiency, there has thus been re-evaluation of the long-held prohibition against T therapy in men with PCa. Indeed, a growing literature indicates that some men may do well with such treatment, without a high rate of PCa progression as had been long assumed in the past.

Modern data have provided strong evidence that serum androgens, especially T and DHT, are unrelated to PCa risk. The endogenous Hormones and Prostate Cancer Collaborative Group combined results from 18 longitudinal studies from around the world to arrive at a dataset of 3886 men who developed PCa with a control group of 6448 men who did not.6 Baseline serum levels of a number of sex steroids as well as other hormones were stratified by quintiles. No significant relationship was seen for any of the sex steroids, including T, free T, and DHT. Specifically, men with the highest serum T and DHT concentrations were at no greater risk of developing PCa than men with the lowest concentrations.

In the placebo arm of the REDUCE trial, Muller et al.19 investigated whether baseline serum T or DHT predicted development of PCa. In this study, 3255 men in the placebo arm underwent protocol-driven prostate biopsies at years 2 and 4 following entry, regardless of PSA value. No significant association was observed between PCa diagnosis and serum T or DHT. Indeed, at the very highest levels of serum T concentration a trend toward a reduced rate of PCa diagnosis was noted.

Cui et al.20 performed a meta-analysis of 22 randomized controlled T trials to determine whether men who received T were more likely to develop PCa than men who received placebo. The study population consisted of 2351 men. There were eleven trials of <12 months duration, and eleven trials of 12–36 months duration. The results of this study revealed that T administration was unrelated to PCa development.

Testosterone therapy following radical prostatectomy
A modest number of case series have reported results of T therapy in men following radical prostatectomy (RP). Kaufman and Graydon in 2004 reported no recurrences in 7 men treated with T for 2–13 years following RP.27 Six had Gleason 6 disease and 1 had Gleason 7 disease. Agarwal and Oefelein reported no biochemical recurrences in 10 men with T therapy after RP.28 This series included a number of men with higher risk disease, including 7 with Gleason 7 disease, and 1 with Gleason 8 pathology. The remaining 2 had Gleason 6 disease. Follow-up was 1–11 years.

In 2009 Khera et al.29 reported results for a larger group of 57 patients. The study population included men with Gleason 6 (n = 24), Gleason 7 (n = 26), and Gleason 8 cases (n = 4). With a mean follow-up of 13 months (range: 1–99), no biochemical recurrences were observed.

The largest series to date investigated 103 cases of men treated with T following RP.30 This series was notable for inclusion of 26 patients at high risk for biochemical recurrence, based on Gleason 8–10, positive surgical margins, or positive lymph nodes. A comparison group was composed of 49 men that underwent RP, but did not receive T therapy. This group included 15 high-risk cases. Mean follow-up was 27 months. Biochemical recurrence rates were 4% in the T-treated group and 16% in the untreated comparison group.

Although the total number of men treated with T following RP is small, and no prospective, controlled studies have yet been performed, these results do suggest that T therapy in men following RP is not associated with high rates of biochemical recurrence in the short to moderate term.

Testosterone therapy following radiation treatments
In 2006 Sarosdy reported on results of T therapy in 31 men who had
undergone brachytherapy for definitive treatment of localized PCAs. Twenty underwent brachytherapy alone and eleven were treated with a combination of brachytherapy and external beam radiation therapy (XRT). Fourteen of the treated men also underwent adjuvant androgen deprivation therapy (ADT) at the time of treatment. The study population included 22 men with Gleason < 6 (n = 24), 6 men with Gleason 7, and 3 men with Gleason 8 or 9. Mean duration of T therapy was 4.5 years, with a mean follow-up of 5 years (range: 1.5–9 years). None of the men developed biochemical recurrence, and all had PSA levels < 1 ng ml\(^{-1}\) at last follow-up, including 74% with PSA < 0.1 ng ml\(^{-1}\).

A small series of 5 men was reported by Morales et al. These men received T therapy following prostate biopsies, with definitive treatment reserved for men with evidence for disease progression or more aggressive tumor grade. Approximately one-third of men ultimately show signs of T therapy in men following previous PCa diagnosis. This study captured approximately 97% of PCa diagnoses in the US between 1991 and 2007, and the study investigated approximately 350,000 newly diagnosed cases of PCa. No association was found between T therapy usage and PCa grade, stage, or survival. Examination of the same database in 2014 was performed to assess use of T therapy in men following previous PCa diagnosis. T therapy in men with previously diagnosed PCa was more common in men who were better educated, wealthier, younger and in those who underwent surgical treatment rather than radiation, medical management, or active surveillance. Overall as well as PCa-specific mortality rates were slightly lower for men treated with T compared with untreated men, at 5.4% vs. 6.9% overall and 0.9% vs. 1.6% PCa-specific, respectively. These differences did not reach statistical significance. The use of T therapy was not associated with increased risk of subsequent ADT, suggesting that treatment did not appreciably contribute to development of advanced or metastatic disease. A small number of studies have now explored the use of T therapy as a therapeutic cancer treatment in men with advanced PCa. Szmulwitz et al. reported their experience with high-dose T therapy combined with 5-alpha reductase inhibitors in 96 men with T deficiency and PCa. This was a heterogeneous group that included men with localized PCa, failures following definitive local treatment (RP, XRT, brachytherapy), and men with documented metastatic disease. Target serum T concentrations were 1800–3000 ng dl\(^{-1}\), and mean concentration achieved was 1391 ng dl\(^{-1}\). Gleason score was 8 or higher disease in 24%. Only 43% of this group had PSA progression. Thirty-one of the 96 men continued on T therapy throughout the study period.

Ferreira et al. reported on the results of T therapy in a group of 5 men that had undergone surgical castration for advanced PCa, all with negative bone scans. Pathology in these men was Gleason 7 in 2 men, Gleason 8 in 2, and Gleason 9 in 1. Baseline PSA ranged from 1.9 to 4.1 ng ml\(^{-1}\) despite castration. Treatment with T was provided by intramuscular injection, with good clinical response. After 1 year of treatment all patients had serum PSA < 10 ng ml\(^{-1}\) with negative bone scans. At 18 months serum PSA for one patient rose over 10 ng ml\(^{-1}\), resulting in cessation of T therapy. His PSA subsequently decreased by approximately 50%.

In 2013, Kaplan and Hu investigated the SEER-Medicare database to assess the impact of T therapy on subsequent PCa diagnosis. This database captured approximately 97% of PCa diagnoses in the US between 1991 and 2007, and the study investigated approximately 350,000 newly diagnosed cases of PCa. No association was found between T therapy usage and PCa grade, stage, or survival. Examination of the same database in 2014 was performed to assess use of T therapy in men following previous PCa diagnosis. T therapy in men with previously diagnosed PCa was more common in men who were better educated, wealthier, younger and in those who underwent surgical treatment rather than radiation, medical management, or active surveillance. Overall as well as PCa-specific mortality rates were slightly lower for men treated with T compared with untreated men, at 5.4% vs. 6.9% overall and 0.9% vs. 1.6% PCa-specific, respectively. These differences did not reach statistical significance. The use of T therapy was not associated with increased risk of subsequent ADT, suggesting that treatment did not appreciably contribute to development of advanced or metastatic disease. A small number of studies have now explored the use of T therapy as a therapeutic cancer treatment in men with advanced PCa. Szmulwitz et al. reported a phase 1 study in which 15 men with castration resistant PCa (CRPC) and baseline PSA of 11 received treatment with transdermal T at various doses to achieve median T concentrations of approximately 300 ng dl\(^{-1}\) from baseline castrate levels. Only one patient developed symptomatic progression, and three patients demonstrated a decline in PSA. Similarly, Morris et al. treated 12 men with CRPC with transdermal T. No pain flares were seen, only one patient came off study, and PSA declined in one patient by > 50%.

**DISCUSSION**

There has been a revolutionary change in concept and practice with regard to the use of T therapy in men with PCa over the last 10–15 years. The long-taught idea that raising serum T necessarily causes rapid and universal growth of existing PCa has been found to be untenable. Prostate size and PSA do not correlate with serum androgen concentrations in the general population, treatment
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with supraphysiologic T concentrations for periods up to 9 months do not result in increases in PSA or prostate volume,\(^4\) and men with the highest serum T or DHT concentrations are at no great risk of developing PCa than men with the lowest serum androgen concentrations.\(^{4,19}\)

The old beliefs were based on the historical observation that castration and estrogen treatments in men with metastatic PCa lowered serum PSA and serum acid phosphatase. Further, men on intermittent androgen deprivation routinely demonstrate a rise in PSA in concert with rising serum T when ADT is discontinued. These disparate observations are explained and unified by the saturation model, based on evidence that there is a finite, limited ability of androgens to stimulate prostate growth. This conceptual framework has set the stage for a modest number of studies reported here in which men with PCa have received T therapy.

Although large clinical studies are required to demonstrate the safety of T therapy in men with PCa, we also note the remarkable consistency of the benign outcomes in the various reported studies. At a minimum, the evidence are sufficient to conclude that T therapy does not necessarily cause rapid, universal tumor growth in most men with PCa. Further investigation is required to assess overall safety, and which populations of men may be reasonable candidates for treatment.

There may even be a rationale for using T therapy as a treatment for advanced PCa. Denmeade and Isaacs suggest that based on preclinical data in which supraphysiological T concentrations inhibited growth of castrate resistant PCa xenografts, high T concentrations in men may provide a therapeutic cancer benefit due to altered androgen receptor expression.\(^8\)

The argument for T therapy in general has grown stronger over time, with increasing evidence of improvement in bothersome symptoms, as well as benefits relating to general health, particularly cardiometabolic disease.\(^9\) With so many men now being diagnosed with PCa, including younger men in their 40s and 50s, it may no longer be reasonable to deprive these men of a treatment that may provide important benefits, and improved quality of life, based on a prohibition against T therapy that originated in an era when our understanding of the biology of PCa was in its infancy. We are unaware of any large controlled study demonstrating that T therapy is associated with increased PCa-related risks. The absence of such a study does not guarantee safety, but is worth considering when faced with such a strong prohibition.

From discussions with colleagues around the world, there has been a clear change in behavior, as it is no longer rare for urologists and other specialists to offer T therapy to men with PCa. We offer the following comments and suggestions to healthcare providers considering this option.

1. Given the uncertainty of risks, we recommend limiting treatment with T to those with clear potential for benefits, namely those who are symptomatic.
2. The safest group to offer T therapy consists of men with undetectable PSA 1–2 years following RP for Gleason 6 disease or lower. These men are at low risk for developing PCa recurrence.
3. Somewhat more risky are men following XRT or brachytherapy, since the possibility exists of residual in situ PCa. These men often have low but detectable PSA levels, and PSA concentrations may fluctuate from time to time. If PSA rises, it may well be assumed by patient and healthcare providers that increased T was responsible.
4. The most risky group is men with advanced, recurrent, or metastatic disease. It is to be expected that PSA will rise in these men over time, regardless of whether they receive T therapy. Many will eventually die from PCa. Any evidence for disease progression in the setting of T therapy will be attributed by others to higher T. We strongly caution against the use of T therapy in these populations, except in an investigational setting.
5. Men on active surveillance also represent a high risk group. Published reports indicate that approximately 25%–30% of men on active surveillance protocols will demonstrate disease progression over 3–5 years, even without T therapy. Those prescribing T therapy may be held responsible for disease progression even if this would have occurred without treatment.
6. Men with serum T concentrations below the saturation point (approximately 250 ng dl\(^{-1}\) or 8 nmol l\(^{-1}\)) are likely to demonstrate a rise in PSA with T therapy. This occurs because serum PSA in a T-deficient man is falsely depressed. The magnitude of the PSA increase will be greater for men substantially below the saturation point than for men with serum T only slightly below it. PSA will usually stabilize after 3–6 months of T therapy. A continued rise beyond 6 months is worrisome for advancing disease.
7. Use extreme caution in men currently on ADT, particularly if ADT had been instituted to treat metastatic disease. The likelihood is that whatever initial clinical benefits had accrued from ADT will be reversed with T therapy, with the possibility of even greater disease progression. This is the population that demonstrated a high rate of disease progression, usually within 30 days, in older studies leading to the subsequent prohibition against T therapy in all men with PCa. For men on ADT for minimal or localized disease (e.g. no metastases or nodal disease, low Gleason score), consideration should first be given to a trial off ADT, as this will adequately resolve symptoms of T deficiency in many men without resorting to exogenous T treatments.
8. Patients must be advised that T therapy in men with PCa has not been adequately studied to provide any assurances of safety, and that treatment involves risk of PCa progression or recurrence, and death.
9. We recommend a signed informed consent from all individuals who wish to undergo T therapy after a diagnosis of PCa, regardless of prior treatment or likelihood of cure.

As with any medical treatment, clinicians must weigh the likely benefits against its risks. Given the troubling symptoms and associated health implications of T deficiency in men, and our new knowledge of the biology of androgens and PCa, this calculus has changed dramatically in recent years. In our practice, we have now treated well over 200 men with T therapy after a variety of PCa treatments, including a substantial number on active surveillance. Our experience is that many of these men are willing to accept the theoretical risks of treatment, and are grateful for the opportunity to live a fuller and happier life. Although it must be emphasized to patients that safety data are lacking, on multiple occasions we have heard the same refrain after T therapy: “Doctor, I’d rather live 3 years feeling this way than 10 years the way I felt before treatment.”

CONCLUSIONS
Recent and accumulating evidence now strongly challenges the longstanding prohibition against the use of T therapy in men with a history of PCa. The saturation model explains why changes in serum androgen concentrations cause large changes in PCa behavior at very low concentrations, but not within the physiological range. This provides a conceptual framework for understanding the largely benign reported experiences of T therapy in men with PCa. These
promising early observations justify larger, prospective trials to assess clinical outcomes and safety of T therapy in the setting of PCa.

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