Testosterone replacement therapy (TRT) and prostate cancer: An updated systematic review with a focus on previous or active localized prostate cancer

Louis Lenfant, Priscilla Leon, Géraldine Cancel-Tassin, Marie Audouin, Frédéric Staerman, Morgan Rouprêt, Olivier Cussenot

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Lenfant L[5], Leon P[1-2], Cancel-Tassin G[2-3], Audouin M[2], Staerman F[4], Rouprêt M[2-3-5], Cussenot O[2-3].

1. Service d'urologie, Clinique Pasteur, Royan, France

2. GRC n°5 PREDICTIVE ONCO-UROLOGY, Sorbonne Université, AP-HP, Hôpital Tenon, F-75020 Paris, France

3. CeRePP, F-75020 Paris, France

4. Service d'urologie et d'andrologie de la polyclinique de Reims – Bezannes, Reims, France

5. Urology department, Sorbonne University, GRC n°5, PREDICTIVE ONCO-UROLOGY, AP-HP, Hôpital Pitié-Salpêtrière, 83 Boulevard de l'Hôpital, F-75013 Paris, France

First two authors contributed equally to this paper

Corresponding author :

Louis Lenfant, MD

Sorbonne Université, GRC no 5, ONCOTYPE-URO, AP-HP, Hôpital Pitié-Salpêtrière, 83 Boulevard de l'Hôpital, 75013 Paris, France.

louis.lenfant@aphp.fr

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Abstract

Introduction: Often contraindicated because of the theoretical risk of progression based on the dogma of hormone dependent prostate cancer (PCa), Testosterone replacement therapy (TRT) is increasingly discussed and proposed for hypogonadal patients with localized prostate cancer.

Purpose: To perform a systematic literature review to determine the relationship between Testosterone replacement therapy (TRT) and the risk of prostate cancer with a focus on the impact of TRT in the setting of previous or active localized prostate cancer.

Material and Methods: As of October 15, 2019, systematic review was performed via Medline Embase and Cochrane databases in accordance with the PRISMA guidelines. All full text articles in English published from January 1994 to February 2018 were included. Articles were considered if they reported about the relationship between total testosterone (TT) or bioavailable testosterone (BT) and prostate cancer. Emphasis was given to prospective studies, series with observational data and randomized controlled trials. Articles about the safety of the testosterone therapy were categorized by type of PCa management (active surveillance or curative treatment by radical prostatectomy, external radiotherapy or brachytherapy).

Results: Until more definitive data becomes available, clinicians wishing to treat their hypogonadal patients with localized prostate cancer with testosterone replacement therapy (TRT) should inform them of the lack of evidence regarding the safety of long-term treatment for the risk of PCa progression. However, in patients without known prostate cancer, the evidence seems sufficient to think that androgen therapy does not increase the risk of subsequent discovery of prostate cancer.

Keywords: testosterone deficiency, testosterone therapy, prostate cancer, hypogonadism, androgen, therapeutics.

Introduction

Since the discovery by Huggins and Hodges [1]of the hormonal dependence of prostate cancer (PCa), more than 75 years ago, the dogma is that testosterone stimulates prostate cancer and that castration reduces metastatic cancers [2]. Thus, the contraindication of androgen therapy in men with a history of prostate cancer is based on the concept of androgen sensitivity of tumor prostate cells, regardless of the testosterone concentration. However, while prostate cancer is extremely sensitive to low levels of testosterone, there is ample evidence that its growth is not influenced by androgens at higher concentrations [3].

This loss of sensitivity to testosterone beyond a certain threshold is most probably explained by the limited ability of the androgen receptor (AR) for its ligand, with a low number of affinity sites already saturated with low testosterone rate. Any AR stimulation beyond this saturation results in few additional physiological effects on benign or malignant prostatic tissues. This saturation model proposed by Morgentaler[3] for the androgen receptor has been observed in other steroid hormone systems. It could explain why serum testosterone does not appear to be related to the risk of prostate cancer in the general population, and why the administration of testosterone in men with metastatic prostate cancer results in a rapid progression of the disease in castrated men, but not in eugonadal men [3]. This statement is not necessarily true in clinical practice as evidenced by the numerous clinical trials of bipolar androgen therapy (high dose androgens administered to patients on ADT) with positive results

The androgen deficiency of the aging male (ADAM) or andropause is a clinical and biochemical syndrome defined by a decrease in testosterone level below the normal range (lower normal limit for young men ranging from 8 to 12 nmol/L depending on laboratories and assays) associated with clinical symptoms appearing with age [4]. This pathological decline is different from the androgen decline that occurs with age but remains in the physiological norm.

Its pathological character comes from the degradation of the quality of life and the impact on the general health related to the physiological action of testosterone on the cardiovascular system, bone mineralization, muscle and fat masses. Clinical signs can be sexual (decreased libido, erectile dysfunction, ejaculation disorders) and/or general (atherosclerosis, metabolic syndrome, decrease in muscle strength and mass, osteoporosis, and decrease in cognitive ability) [4].

Hypogonadism is associated with the development of metabolic syndrome, type 2 diabetes and cardiovascular disease [4]. Hypogonadism can be associated with an increased mortality rate [4]. Therefore, it must always be considered pathological when diagnosed. The growing recognition of the health benefits of exogenous testosterone therapy in men with hypogonadism, is explained by the improvement of energy, vitality, sexual desire, erectile function, body composition and bone mineral density [4].Thus, the beneficial effects of androgen therapy on the symptoms of andropause are demonstrated [5]. Unfortunately, this syndrome is often not taken in consideration by the medical community. Notably, in France, less than 2% of patients are treated, whereas they are 8% and 32% in Germany and in the USA, respectively. So far, the main reason given by physicians for not treating age-related hypogonadism is the risk of developing prostate cancer (51% in 2006 and 55% in 2010, respectively) [6].

Our study aims to determine through existing literature the impact of Testosterone replacement therapy (TRT) in the setting of previous or active localized prostate cancer.

Methods:

A systematic review of PubMed, MEDLINE, EMBASE and Cochrane was conducted for studies about testosterone administration in men with known prostate cancer history, published English languages, between January 1994 and October 21, 2019. Emphasis was given to prospective studies, series with observational data, and randomized controlled trials. This systematic review of the literature was performed following the PRISMA criteria and using the keywords: Testosterone[MeSH Terms]) AND Prostatic Neoplasms[MeSH Terms]) OR Hypogonadism[MeSH Terms]) AND Androgens/deficiency[MeSH Terms] . Based on these criteria, 164 eligible publications were retrieved. After exclusion of articles on animal (8), not published in English or French language or with no abstract (21), 135 publications (10 related to clinical trials) remained. Ninety-two articles corresponding to the theme of this review were retained after reading of the abstracts.

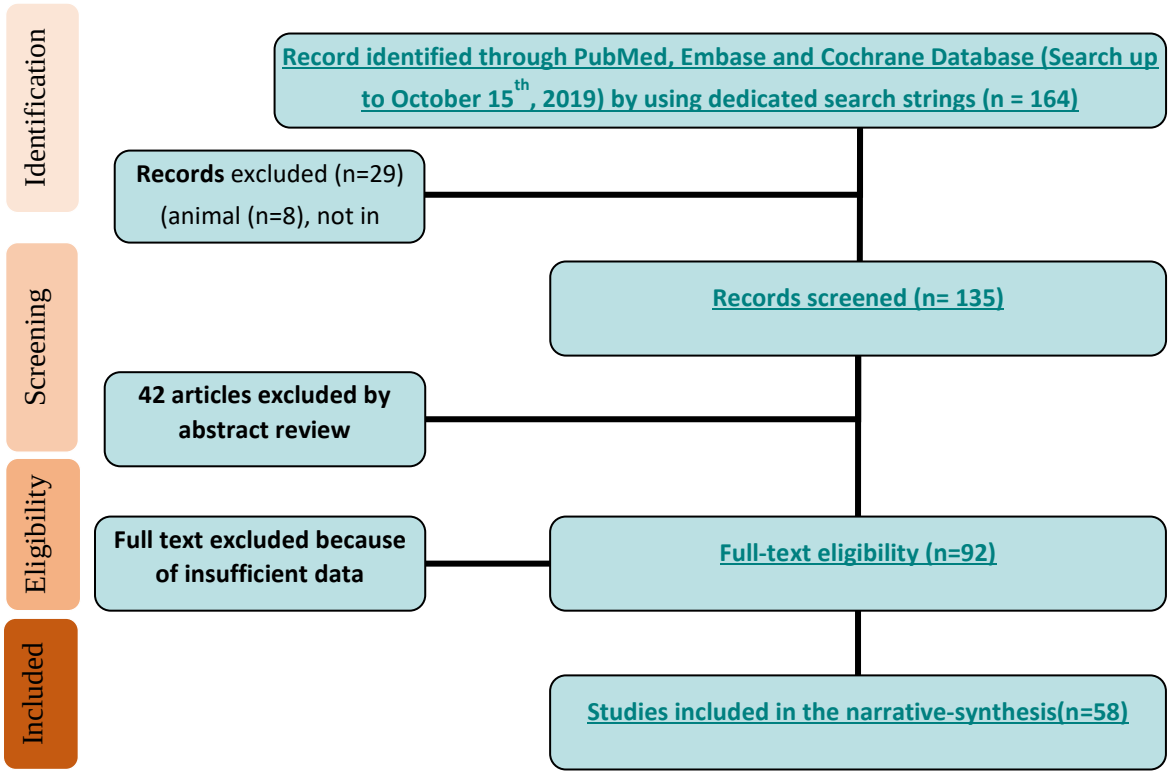

Figure 1: PRISMA Flow diagram. As of October 15th, 2019, a systematic search of the following electronic resources was performed: Medline (via PubMed), Embase (via Ovid) and Cochrane databases. Search strategy relied on the PICO (Patient – Intervention -Comparison – Outcome) criteria and included the following search terms: Testosterone[MeSH Terms]) AND Prostatic Neoplasms[MeSH Terms]) OR Hypogonadism[MeSH Terms]) AND Androgens/deficiency[MeSH Terms]

Study eligibility was determined by P.L and G.C. Disagreement was resolved by a third party (L.L).

Results were organized into five parts arranged in a logical and coherent order.
First, we presented the existing clinical evidence against Huggins' dogma. The second part is about the relationship between testosterone level and the risk of prostate cancer. The third part deals with the relation between testosterone replacement therapy (TRT) and PCa risk. The fourth part examines the effect of testosterone therapy in PCa patients. In this last section, articles about testosterone treatment were analyzed separately according to the type of management of PCa (active surveillance or patients with a history of treatment for prostate cancer).

Table 1 summarizes these studies, showing the risk of exogenous administration of testosterone in patients with PCa, treated or under active surveillance. In the last section, we summarized recommendations and proposals for testosterone replacement therapy in relation with prostate cancer.

Results

1. Clinical evidence against Huggins' dogma:

1.1 The Use of 5 alpha reductase inhibitors reduces the risk of PCa

Five alpha reductase Inhibitor (5 ARI), are enzymes that convert testosterone into its active metabolite, dihydrotestosterone (DHT). This treatment provides a selective form of androgen deprivation by severely reducing intracellular concentrations of DHT. Using these 5ARI for 3 to 12 months would reduce, but to a lesser extent than castration, the PSA level (approximately 50%) and prostatic volume (by one third) [7]. The Prostate Cancer Prevention Trial (PCPT) showed that compared to placebo, finasteride (5ARI type 2) decreased by about 25% the risk of prostate cancer in men ≥ 55 years with a PSA <3.0 ng / mL [8]. The REDUCE trial showed a showed a 22.8% relative risk reduction in prostate cancer cases diagnosed during a 4-year treatment period with dutasteride (5 ARI type 1 and 2). This result implies that DHT has a greater role than testosterone in the development of prostate cancer [9].

1.2 Absence of correlation between serum testosterone and PSA levels in eugonadal men

Grober et al. showed no significant correlation between PSA and total serum testosterone levels in 385 eugonadal, 229 untreated hypogonadal and 229 hypogonadal men receiving testosterone [10]. Moreover, PSA levels did not increase statistically or clinically following testosterone treatment.

A randomized study including 43 men showed no significant increase in PSA level in patient treated with testosterone enanthate intramuscular injection (600 mg / week) vs. placebo. Another randomized study of 31 young healthy men showed no significant change in the prostate volume or PSA level regardless of the exogenous testosterone dose (100, 250, or 500 mg of intramuscular testosterone once a week for 15 weeks). Finally, a 2-year treatment of testosterone in eugonadal men didn't affect prostate volume or PSA level despite supraphysiological blood levels [11].

2. Association between testosterone level and the risk of PCa or aggressive PCa

2.1 Testosterone level and risk of PCa

With age, the incidence of prostate cancer increases as testosterone levels decrease [12]. The Massachusetts Male Aging Study (MMAS) found a 10% and 24% decrease in free and total testosterone levels per decade respectively. On the other hand, PCa is rare before age 40, and about 6 cases in 10 are diagnosed in men aged 65 or older. Data collected by Mohr et al. [13] , on more than 1,500 men showed no significant correlation between the risk of PCa and androgens concentration. Seventeen serum hormones, including androgens, estrogens, and adrenal and pituitary hormones, were measured at baseline (1987-1989) and used to predict incident prostate cancer by follow-up (1995 to 1997) using data from the Massachusetts Male Aging Study. Seventy men (4%) on 1576 were diagnosed with prostate cancer between the baseline and follow-up periods (approximately 8 years). None of the hormones was associated with PCa risk, except for androstanediol glucuronide (AAG) [13].

Testosterone concentration has been shown to be significantly lower in patients with PCa than in those with benign prostatic hypertrophy, making it an independent predictor of this cancer. Among 345 consecutive hypogonadal men with a PSA level of 4.0 ng/mL or less, PCa was detected in 21% of men with a testosterone level of 250 ng/dL or less compared with 12% of men with a testosterone level greater than 250 ng/dL ($p = 0.04$) [14]. Low free testosterone level was significantly associated with the presence of adenocarcinoma in the re-biopsy after high-grade prostatic intraepithelial neoplasia (HGPIN) [15]. A collaborative analysis of 18 prospective studies including 3866 men with PCa and 6438 controls found no association between the PCa risk and serum concentration of testosterone [16]. In the placebo arm of the REDUCE trial, the risk of prostate cancer was not correlated to the level of total testosterone or DHT [9]. However,

patients who had the lowest levels of testosterone (<10 nmol / L or 288 ng / mL) appeared to have a lower prostate cancer frequency, in agreement with the saturation model.

2.2 Testosterone level and aggressiveness of prostate cancer

Low testosterone level is associated with aggressiveness of PCa at different stages of the disease:

2.2.1. *At initial diagnosis, a higher testosterone level is associated with a lower clinical stage, a lower PSA level and a lower risk of progression* [17]. In this study performed on 137 patients diagnosed with prostate cancer, the testosterone level was also inversely correlated with bilateral cancer ($p < 0.01$) and tumor percentage on biopsies ($p < 0.01$). In multivariate analysis, age and low testosterone were associated with a higher risk of progression (as classified by D'Amico). In a study including 812 patients, Albisinni et Al showed that neither total nor free testosterone were associated with a higher Gleason score [18]. However in the same study , the percentage of free / total testosterone levels was correlated with an increased frequency of prostate cancer with a Gleason score ≥ 7 [18]. In a large Sweden study including 38,570 prostate cancer cases and 192,838 age matched controls, patients who received TRT (1% of the cases and controls) had more favorable-risk prostate cancer and lower risk of aggressive prostate cancer in multivariate analyses [19].

2.2.2. *Low serum pretreatment testosterone level is correlated with an extra-prostatic disease and positive margins* [20]. Massengill et al. performed a study on 879 patients with localized prostate cancer treated with radical prostatectomy (RP), and observed that patients with non-organ confined prostate cancer (pT3-T4) showed significantly lower pretreatment total testosterone levels than those with organ confined cancer (pT1-T2) ($p = 0.041$)[20]. In multivariate analysis, preoperative total testosterone was a significant independent predictor of extraprostatic disease, but not of biochemical recurrence. In a single-center cohort of 673

consecutive Caucasian European patients who were treated by RP, Salonia et al. showed that a low total testosterone was associated with an higher risk of seminal vesicles invasion [21]. In multivariate analysis, only total circulating testosterone less than 1 ng / mL remained an independent predictor of seminal vesicle invasion ($p = 0.006$) whereas total testosterone was no longer an independent predictor of extracapsular extension, seminal vesicle invasion or high grade PCa.

Porcaro et al. found that the pretreatment total PSA to free testosterone (FT) ratio ≥ 0.40 was highly correlated with aggressive stages (pT3b + pT4) and high Gleason scores (8 + 9) [22][. In a study performed on 374 patients treated by radical prostatectomy, low bioavailable and free testosterone levels, were associated with a higher risk of developing high grade PCa ([OR] = 1.76; $p<0.001$ and OR = 1.39; $p<0.001$, respectively) [25].

2.2.3. *Testosterone deficiency is associated with PCa aggressiveness*

Recent AndroCan Clinical trial including 1343 patients with localized PCa scheduled to undergo radical prostatectomy showed that Testosterone deficiency (defined by TT and/or BT levels) was independently associated with higher PCa aggressiveness[23]. Bioavailable testosterone BT was also a predictive factor for predominant Gleason pattern 4 disease.

2.2.4. *Biochemical recurrence is more common in patients with low preoperative testosterone level*. Yamamoto et al. [24] showed that preoperative testosterone level was an independent predictor of biochemical recurrence after radical prostatectomy (RP) ($p = 0.021$), along with the Gleason score of the prostatectomy specimen ($p = 0.006$), surgical margin status ($p = 0.0001$), and preoperative PSA level ($p = 0.0001$). Survival rate without biochemical recurrence at five years was worse in patients with low preoperative testosterone (67.8%) compared to those with normal testosterone (84.9%) ($p = 0.035$) [24]. This study showed that the testosterone level increased after RP ($p <0.0001$), with a larger increase seen in the group with low preoperative testosterone level ($p = 0.0003$).

This association between low testosterone level and risk of biochemical recurrence could be explained by the production of inhibin-alpha by prostate tumor cells having a negative feedback on the hypothalamic-pituitary axis. Indeed, PCa patients with a higher expression of inhibin α subunit on RP tumor tissue had a higher risk of recurrence after RP, although this association was not statistically significant [25]. This hypothesis would also explain the improvement in testosterone level after radical prostatectomy.

3. Hypogonadal men treated with testosterone therapy and risk of PCa

3.1 Testosterone replacement treatment (TRT) of hypogonadal men does not modify PSA level at long term

Sixty percent of patients treated for androgen deficiency in aging male (ADAM) had a rising PSA level between 17 and 40% in the first months after the start of treatment [26]. This response varied between patients and 40% of them had no variation in PSA level. Khera et al. studied the evolution of PSA level in 451 hypogonadal men treated with testosterone for 12 months and found that the increase in PSA depended on the baseline testosterone level. Indeed, patients with baseline total testosterone (TT) < 250 ng / dL had a significant increase in PSA after treatment with exogenous testosterone unlike patients with baseline TT ≥ 250 ng / dL [27]. Moreover, no significant increase in PSA level was found after 24 months, when compared with the baseline level at the initiation of the treatment. Similarly, a systematic review including 44 studies concluded that testosterone therapy did not have a significant effect on serum PSA levels [28].

Little or no change in prostate volume, urine flow, postvoiding residual urine and prostate voiding symptoms have been reported in patients treated for ADAM [29]. Although one study showed that the International Prostate Symptom Score (IPSS) decreased during the treatment period, all the others reported no change of the IPSS [26-28]. In a meta-analysis of 14

studies involving 2,029 men with a mean follow-up of 34 months, no statistically significant difference in IPSS between initial treatment and follow-up was observed in men treated with TRT compared with those receiving placebo.

3.2 Patients treated for ADAM do not develop more prostate cancer than the general population.

The UK Androgen Study is a prospective observational cohort of 1,365 men with symptomatic androgen deficiency treated with exogenous testosterone and followed for up to 20 years. Fourteen prostate cancers (1% of patients) were diagnosed during the follow-up and this incidence was equivalent to that expected in the general population [32]. Similarly, Haider et al. studied the incidence of PCa among 1,023 hypogonadal men from 3 independent prospective studies who were treated with testosterone. PSA and prostate volume increased during follow up but the incidence of PCa among this cohort was lower than that seen PCa screening trials [33]. In a recent observational prospective study of 805 hypogonadal men, Saad et al. reported that long-term treatment with testosterone undecanoate injections alleviated erectile dysfunction and reduced the risk of major adverse cardiovascular events, prostate cancer, and mortality [30].

3.3 Patients treated for ADAM do not develop more prostate cancer than untreated men.

A recent study using the UK clinical practice research datalink including 12,779 men with late-onset hypogonadism reported that the use of TRT was not associated with an overall increased risk of prostate cancer compared with nonuse [31]. A, randomized, double-blind controlled study including 44 hypogonadal men treated with intramuscular injection of testosterone (150 mg) or placebo every 2 weeks for 6 months showed no significant change in prostate tissue levels of testosterone or DHT in the treated groups, despite normalization of their serum testosterone levels [29]. Analysis of the data extracted from the multi-national Registry of

Hypogonadism in Men (RHYME) who included testosterone treated or untreated hypogonadal men, showed that the proportion of positive biopsies was nearly identical in treated and untreated groups [28] . A meta-analysis of 11 randomized placebo-controlled trials (nine with follow up of one year or less) found that prostate cancer rate was similar between testosterone and placebo groups (1.3% vs. 1.5%)[32] . Similarly, a meta-analysis of 19 studies with 651 men treated with testosterone versus 433 men treated with placebo, did not find a statistically significant difference in terms of rate of prostate cancer between the two groups [33].

According to the Surveillance, Epidemiology, and End Results-Medicare (SEER) data, 2,237 (1.5%) of 149,354 patients diagnosed with prostate cancer from 1992 to 2007 were under androgen therapy at diagnosis[34]. These patients' diseases were less often high grade or locally advanced than those of men without testosterone replacement therapy (TRT) [34]. Moreover, no significant difference in either overall or cancer-specific survivals was found between these two groups of patients. However, men treated by TRT have more medical care and more PCa screening tests than untreated men. Maybe because of this potential measurement bias, two studies have shown a statistically significant reduction in the risk of prostate cancer mortality (relative risk = 0.80; confidence interval 95%, 0.65 to 0.98) in patients treated with TRT [34, 35].

Finally, in response to widespread concerns about the treatment with exogenous testosterone for male hypogonadism, an international conference of consensus of experts was convened[36]. Nine resolutions were debated, with unanimous approval that the evidence doesn't allow demonstrating an increased risk of PCa with exogenous testosterone treatment.

4. Patients with localized prostate cancer may benefit from androgen therapy without compromising their chance of curing cancer

4.1 Patients treated for localized PCa and androgen therapy

Retrospective series focused on monitoring the possible biochemical recurrence after radical prostatectomy on a population treated with androgens for ADAM found no or very few recurrences even after 12 years of follow-up [37-45] (Table 1). The same observation was made in patients who received curative treatment with brachytherapy or external beam radiotherapy (Table 1) [38, 46-49].

4.2 PCa patients on active surveillance and androgen therapy

This situation is increasingly common for low-risk prostate cancer. Active surveillance reports third stop after one year of monitoring for histological progression and / or PSA [51]. Only few studies have analyzed the PCa progression after testosterone replacement therapy: two observed no clinical progression [47] whereas the other ones found between 8 and 15 % of patients with increase in Gleason score [50-53] (Table 2).

5. Recommendations for androgen therapy

Currently, no definitive recommendation has been made for the administration of androgen therapy to patients with prostate cancer [54].

5.1. Existing recommendations that concern prostate cancer risk are:

5.1.1. Recommendations of the American Endocrine Society (2018) at the initiation of androgen therapy and during the treatment [55]

The latest update of the recommendations (2018) highlighted the importance of an appropriate diagnostic work up and monitoring plan. Men should be evaluated for the possibility of previously undiagnosed prostate cancer. A man over 50 years (or over 40 years if he is African American or has a history of prostate cancer in a first-degree relative) should have a digital rectal examination and a serum PSA measurement. If a prostate nodule is detected or the PSA is >4 ng/mL or >3 ng/mL in a man of high risk, the man should be referred for urologic

consultation.

5.1.2 Recommendations of the International Society of Andrology; International Society for the Study of Aging Male; European Association of Urology; European Academy of Andrology; American Society of Andrology for androgen therapy of patients with localized prostate cancer [56] .

Men successfully treated for prostate cancer and suffering from confirmed symptomatic hypogonadism are potential candidates for testosterone substitution after a prudent interval, if there is no clinical or laboratory evidence of residual cancer. As long-term outcome data are not available, clinicians must exercise good clinical judgment together with adequate knowledge of advantages and drawbacks of testosterone therapy in this situation (Level 2b, Grade C). The risk and benefits must be clearly discussed with and understood by the patient and the follow-up must be particularly careful.

5.1.3 Recommendations of the European Academy of Andrology (2020)[57]

Before initiation of TRT in men >40 years of age, the EAA recommends « checking prostate specific antigen (PSA) and performing digital rectal examination (DRE) of the prostate in order to minimize the risk of prescribing T to patients with undiagnosed prostate cancer ». They also recommend « performing digital rectal examination and checking PSA at 3 to 12 months for men >40 years of age after initiating T treatment »

5.2 Pragmatical proposals for androgen therapy (*authors' own recommendations based on the current systematic review*):

In the absence of prostate cancer, the recommendations from the American Endocrine Society [56] must be followed.

In the presence of known prostate cancer, patients with high risk localized disease, positive surgical margins, positive lymph node or metastatic prostate cancer should not be treated by androgen therapy.

This treatment may be initiated for non-high-risk localized prostate cancer (Gleason score < 8, pT1-2, preoperative PSA < 10ng/mL) hypogonadal patient at different time depending on the PCa treatment. For low-risk localized PCa patients (Gleason score < 7, pT1-2, preoperative PSA < 10ng/mL) on active surveillance, TRT could directly be proposed and followed as long as the patient still meet the active surveillance criteria. After RP, postoperative PSA level should be undetectable in order to initiate TRT. The European Association of Urology (EAU) recommends starting TRT the first year after surgery [58]. In case of brachytherapy, TRT should be started after the PSA nadir is reached. The problem is more complex after external radiotherapy, because there is still prostate tissue and serum PSA level does not reach its nadir immediately. For this reason, the proposal of treatment with exogenous testosterone should be made when the level of serum PSA is under 1 ng / mL [56].

All this evidence should be interpreted in light of the study limitations. This review includes many studies with small sample sizes. Some of the studies are retrospective, weakening the level of evidence. Evidence to fully support the safety of TRT in the context of active or treated prostate cancer is still scarce.

Conclusion

For patients without known prostate cancer, evidence seems sufficient to suggest that androgen therapy does not increase the risk of subsequent prostate cancer discovery. Although no controlled studies to date have been conducted to document the safety of androgen therapy in men with prostate cancer, the available evidence suggests that such treatment does not increase the risk of recurrence or progression of PCa. The risk of PCa recurrence after administration of

testosterone is likely to be lower in patients whose initial cancer met low risk criteria and whose PSA was under control for at least four years prior to initiation of testosterone therapy.

Until more definitive data is available, clinicians who wish to offer the benefits of testosterone therapy to their hypogonadal patients with PCa should inform them on the lack of evidence on the safety of long-term treatment for the risk of PCa progression and should document informed consent prior to treatment. The relative risk of hypogonadism and the risk of cancer recurrence in each patient on active surveillance must be evaluated jointly by an endocrinologist, and an oncologist or a urologist. The complete restaging, including new prostate biopsies should be considered before starting testosterone replacement therapy. A plan agreed for monitoring increased PSA should be instituted during testosterone replacement therapy. The circulating testosterone level should be kept as low as possible to meet the replacement needs of each patient.

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Table 1. Published series on testosterone replacement therapy in men treated for prostate cancer.

Reference	Number of patients	Stage or risk	Gleason score	Median/Mean preop PSA (ng/mL)	Treatment	Follow up in months	Definition of biochemical recurrence	Biochemical recurrence (N)
Kaufman et al. [40]	7	NR	Gleason 6 (N = 6) Gleason 7 (N =1)	5.20	RP	18 (12-144)[a]	PSA was less than 0.1 ng/m	0
Agarwal et al. [37]	10	NR	Gleason 6 (N =2) Gleason 7 (3+4) (N =5) Gleason7 (4+3) (N =2) Gleason 8 (4+4) (N =1)	7.0	RP	19 (9-29)[a]	PSA < 0.1 ng/dL	0
Khera et al. [41]	57	T2 or less	Gleason _6 (N = 24) Gleason 7 (N = 26) Gleason ≥_8 (N = 4)	5.58	RP	13 (1-99)[a]	PSA < 0.1 ng/dL	0
Sathyamoorthy et al. [45]	21	High risk patient	Gleason ≥_8 (N = 8)	NA	RP	12 (NR)[b]	NR	0
Nabulsi et al. [43]	22	T2 (N=21) >T2 (N=1)	Gleason 6 (N=13) Gleason 7 (N=9)	5.9	RP	20 (14-30)[a]	NR	1 (4.5%)
Sarosdy [49]	31	T1b (N=1) T1c (N=20) T2a (N=8) T2b (N=2)	≤ Gleason 6 (N=22) Gleason 7 (N=6) ≥ Gleason 8 (N=3)	5.3	BT	60 (18-108)[a]	<0.1 N=23 (74.2%) <0.5 N=30 (96.7%) <1.0 N=31 (100%)	0
Morales et al. [46]	5	NR	Gleason 6 (N=2) Gleason 7 (N=1) Gleason 8 (N=2)	11.96	EBRT	14.6 (6-27)[a]	NR	0
Davila et al. [38]	20	NR	RP : Mean Gleason : 6.2 EBRT Mean Gleason : 5	RP: 6.05 EBRT : 3.5.	14 RP 6 EBRT	12 (NR)[b] 9 (NR)[b]	NR	0

Pastuszak et al. [48]	13	NCCN low N=4 NCCN inter N=7 NCCN high: 2	Gleason 6 (N=4) (31%) Gleason 7 (N=7) (54%) Gleason 8 (N=2) (15%)	5.8	BT and/or EBRT	40.8 (1.5-147)[a]	Two consecutive increases of PSA of >0.5 ng/ml	0
Pastuszak et al. [44]	103	Non-High risk N= 77 High risk N= 26	Gleason <6 (N=1) (1%) Gleason 6-7 (N=74) (72%) Gleason >8 (N=9) (9) Unknown (N=19) (18%)		RP	27.5 (6.2-189.3)[a]	NR	4 (4%)
Ory et al. [47]	74	D'Amico: Low: N=14 Intermediate: N= 30 High : 30	Gleason 6 (N=24) Gleason 7 (N=39) Gleason 8 (N=7) Gleason 9 (N=4)	NA	50 RT 22 RP 1 BT 1 HIFU AS :	36.5 (NR) 48 (NR) 9 42	**Postop** PSA >0.2ug/L with a second confirmatory PSA of over 0.2ug/L **Post radiation**: a 2ug/L rise over post treatment PSA nadir.	3 (6%) 0 0 0
Matsushita et al. [42]	71	≤T2, 84% T3a, 13% T3b, 3%,	Median Gleason = 7	4.5	RP	19 (9-35)[a]	PSA < 0.1 ng/dL	1 (1.4%)

ADT: androgen deprivation therapy, BT: brachytherapy, HIFU: High Intensity Focused Ultrasound, RP: radical prostatectomy, EBRT: external beam radiotherapy, NR: not reported

[a]Median (interquartile range)

[b]mean (standard deviation)

Table 2. Published series of testosterone replacement therapy in men with untreated prostate cancer.

Reference	Number of patients	Median PSA	Gleason Score	Follow up in months	Definition of clinical progression	Clinical progression after testosterone replacement therapy
Morgentaler et al. [53]	13	5.5 (6.4)	Gleason 6 (N=12) Gleason 7 (N=1)	30 (12-97.2)[a]	Increased Gleason score	No increase in PSA level 2 (15.4%) patients with increase in Gleason score.
Ory et al. [47]	8	3.9	Gleason 6 (N=8)	27 (15-46) [a]	Increased Gleason score	No patients with increase in Gleason score
Kacker et al. [51]	28	3.29 (2.50)	Gleason 6 (N=22) Gleason 7 (N=6)	38.9 ± 18.6[b]	Either an increase in Gleason score or an increase in tumor volume	3 (10.7%) patients with increase in Gleason score 9 (32.1%) patients with biopsy progression (increase in either Gleason score or tumor volume)
Lawrence et al. [52]	24	3.79 (2.65)	Gleason 6 (N=22) Gleason 7 (N=2)	29.2 ± 27.5[b]	Increased Gleason score	8 (33.3%) with increase PSA level 2 (8.3%) patients with increase in Gleason score
Hashimoto et al. [50]	12	4.13 (0.90 – 10.3)	Gleason 6 (N=12)	42.5 (12–125)[a]	Increased Gleason score	7 (58.3%) with increase PSA level 2 (16.7%) patients with increase in Gleason score

[a]Median (interquartile range)

[b]mean ± standard deviation

Table 3. Summary of the actual guidelines and pragmatical guideline proposal for androgen therapy in the setting of prostate cancer

Year	Society / Association	Summary of the guidelines
2020	*EAA*	• TRT contraindicated in men with untreated prostate cancer • Men > 40 : PSA + DRE before TRT
2018	*American Endocrine Society*	• Diagnostic work up and monitoring plan • > 50 years* = DRE + PSA before TRT • Abnormal DRE or PSA >3-4 ng/ml = urology consultation
2008	*ISA; ISSAM; EAU; EAA; ASA*	• TRT possible after PCa treatment without evidence of residual cancer • Risks and benefits must be clearly discussed and understood by the patient
2020	***Pragmatical guidelines proposal for androgen therapy****	• *In the absence of prostate cancer:* ⇨ AES (2018) recommendations should be followed • *Known prostate cancer with:* o High risk localized disease o Positive surgical margins o Positive lymph node o Metastatic disease ⇨ Patient should not be treated with TRT • *Non-high risk localized prostate cancer** after treatment* ⇨ TRT might be initiated: o After RP, if PSA is undetectable o After Brachytherapy, after the PSA nadir is reached o After Radiotherapy, if PSA< 1 ng/ml • *Low risk localized prostate cancer*** with Active surveillance* ⇨ TRT could directly be proposed and followed as long as the patient still meet the active surveillance criteria

* : or over 40 years if he is African American or has a history of prostate cancer in a first-degree relative ; ** :Gleason score < 8, pT1-2, preoperative PSA < 10ng/mL), *** :Gleason score < 7, pT1-2, preoperative PSA < 10ng/mL) ****: authors' own recommendations based on the current systematic review ; RP : radical prostatectomy; PCa : Prostate cancer ; TRT : Testosterone replacement therapy ; *ISA* :International Society of Andrology; *ISSAM* : International Society for the Study of Aging Male; *EAU :* European Association of Urology; *EAA* : European Academy of Andrology; *ASA:* American Society of Andrology