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

3
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1 Abstract

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

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

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

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

22

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

25

1 Introduction

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

9 This loss of sensitivity to testosterone beyond a certain threshold is most probably
10 explained by the limited ability of the androgen receptor (AR) for its ligand, with a low number
11 of affinity sites already saturated with low testosterone rate. Any AR stimulation beyond this
12 saturation results in few additional physiological effects on benign or malignant prostatic
13 tissues. This saturation model proposed by Morgentaler³ for the androgen receptor has been
14 observed in other steroid hormone systems. It could explain why serum testosterone does not
15 appear to be related to the risk of prostate cancer in the general population, and why the
16 administration of testosterone in men with metastatic prostate cancer results in a rapid
17 progression of the disease in castrated men, but not in eugonadal men ³. This statement is not
18 necessarily true in clinical practice as evidenced by the numerous clinical trials of bipolar
19 androgen therapy (high dose androgens administered to patients on ADT) with positive results

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

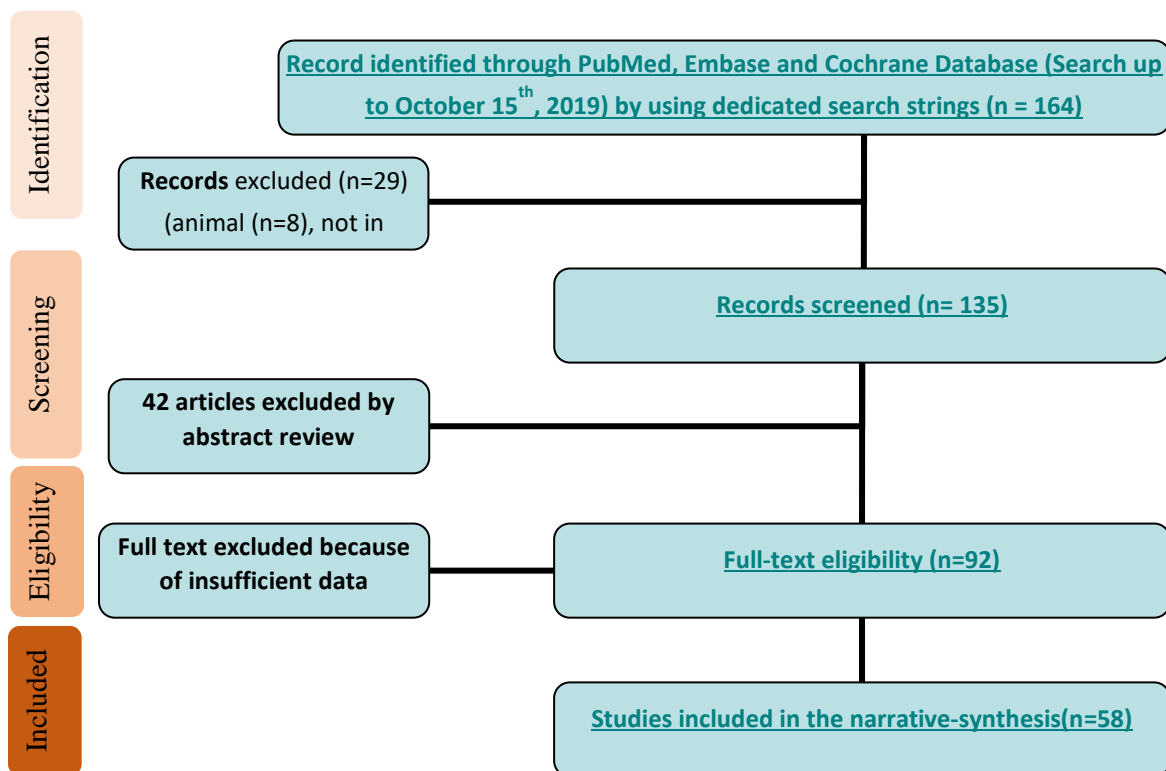
1 Its pathological character comes from the degradation of the quality of life and the impact on
2 the general health related to the physiological action of testosterone on the cardiovascular
3 system, bone mineralization, muscle and fat masses. Clinical signs can be sexual (decreased
4 libido, erectile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

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

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

1 Methods:

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



13

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

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

9 Results were organized into five parts arranged in a logical and coherent order.

10 First, we presented the existing clinical evidence against Huggins' dogma. The second part is
11 about the relationship between testosterone level and the risk of prostate cancer. The third part
12 deals with the relation between testosterone replacement therapy (TRT) and PCa risk. The
13 fourth part examines the effect of testosterone therapy in PCa patients. In this last section,
14 articles about testosterone treatment were analyzed separately according to the type of
15 management of PCa (active surveillance or patients with a history of treatment for prostate
16 cancer).

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

21

22

23 **Results**

1 **1. Clinical evidence against Huggins' dogma:**

2 **1.1 The Use of 5 alpha reductase inhibitors reduces the risk of PCa**

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

13 **1.2 Absence of correlation between serum testosterone and PSA levels in eugonadal men**

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

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

1

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

3 **2.1 Testosterone level and risk of PCa**

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

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

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

3 **2.2 Testosterone level and aggressiveness of prostate cancer**

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

6 *2.2.1. At initial diagnosis, a higher testosterone level is associated with a lower clinical*
7 *stage, a lower PSA level and a lower risk of progression*¹⁷. In this study performed on 137
8 patients diagnosed with prostate cancer, the testosterone level was also inversely correlated with
9 bilateral cancer (p <0.01) and tumor percentage on biopsies (p <0.01). In multivariate analysis,
10 age and low testosterone were associated with a higher risk of progression (as classified by
11 D'Amico). In a study including 812 patients, Albisinni et Al showed that neither total nor free
12 testosterone were associated with a higher Gleason score¹⁸. However in the same study , the
13 percentage of free / total testosterone levels was correlated with an increased frequency of
14 prostate cancer with a Gleason score ≥ 7 ¹⁸. In a large Sweden study including 38,570 prostate
15 cancer cases and 192,838 age matched controls, patients who received TRT (1% of the cases
16 and controls) had more favorable-risk prostate cancer and lower risk of aggressive prostate
17 cancer in multivariate analyses¹⁹.

18

19 *2.2.2. Low serum pretreatment testosterone level is correlated with an extra-prostatic*
20 *disease and positive margins*²⁰. Massengill et al. performed a study on 879 patients with
21 localized prostate cancer treated with radical prostatectomy (RP), and observed that patients
22 with non-organ confined prostate cancer (pT3-T4) showed significantly lower pretreatment
23 total testosterone levels than those with organ confined cancer (pT1-T2) (p = 0.041)²⁰. In
24 multivariate analysis, preoperative total testosterone was a significant independent predictor of
25 extraprostatic disease, but not of biochemical recurrence. In a single-center cohort of 673

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

7 Porcaro et al. found that the pretreatment total PSA to free testosterone (FT) ratio ≥ 0.40
8 was highly correlated with aggressive stages (pT3b + pT4) and high Gleason scores (8 + 9) ²²].
9 In a study performed on 374 patients treated by radical prostatectomy, low bioavailable and
10 free testosterone levels, were associated with a higher risk of developing high grade PCa ([OR]
11 = 1.76; $p < 0.001$ and OR = 1.39; $p < 0.001$, respectively) [25].

12 *2.2.3. Testosterone deficiency is associated with PCa aggressiveness*

13 Recent AndroCan Clinical trial including 1343 patients with localized PCa scheduled to
14 undergo radical prostatectomy showed that Testosterone deficiency (defined by TT and/or BT
15 levels) was independently associated with higher PCa aggressiveness²³. Bioavailable
16 testosterone BT was also a predictive factor for predominant Gleason pattern 4 disease.

17 *2.2.4. Biochemical recurrence is more common in patients with low preoperative*
18 *testosterone level.* Yamamoto et al. ²⁴ showed that preoperative testosterone level was an
19 independent predictor of biochemical recurrence after radical prostatectomy (RP) ($p = 0.021$),
20 along with the Gleason score of the prostatectomy specimen ($p = 0.006$), surgical margin status
21 ($p = 0.0001$), and preoperative PSA level ($p = 0.0001$). Survival rate without biochemical
22 recurrence at five years was worse in patients with low preoperative testosterone (67.8%)
23 compared to those with normal testosterone (84.9%) ($p = 0.035$) ²⁴. This study showed that the
24 testosterone level increased after RP ($p < 0.0001$), with a larger increase seen in the group with
25 low preoperative testosterone level ($p = 0.0003$).

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

7

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

9 **3.1 Testosterone replacement treatment (TRT) of hypogonadal men does not modify PSA** 10 **level at long term**

11 Sixty percent of patients treated for androgen deficiency in aging male (ADAM) had a rising
12 PSA level between 17 and 40% in the first months after the start of treatment ²⁶. This response
13 varied between patients and 40% of them had no variation in PSA level. Khera et al. studied
14 the evolution of PSA level in 451 hypogonadal men treated with testosterone for 12 months and
15 found that the increase in PSA depended on the baseline testosterone level. Indeed, patients
16 with baseline total testosterone (TT) < 250 ng / dL had a significant increase in PSA after
17 treatment with exogenous testosterone unlike patients with baseline TT \geq 250 ng / dL ²⁷.
18 Moreover, no significant increase in PSA level was found after 24 months, when compared
19 with the baseline level at the initiation of the treatment. Similarly, a systematic review including
20 44 studies concluded that testosterone therapy did not have a significant effect on serum PSA
21 levels ²⁸.

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

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

4 **3.2 Patients treated for ADAM do not develop more prostate cancer than the general** 5 **population.**

6 The UK Androgen Study is a prospective observational cohort of 1,365 men with
7 symptomatic androgen deficiency treated with exogenous testosterone and followed for up to
8 20 years. Fourteen prostate cancers (1% of patients) were diagnosed during the follow-up and
9 this incidence was equivalent to that expected in the general population [32]. Similarly, Haider
10 et al. studied the incidence of PCa among 1,023 hypogonadal men from 3 independent
11 prospective studies who were treated with testosterone. PSA and prostate volume increased
12 during follow up but the incidence of PCa among this cohort was lower than that seen PCa
13 screening trials [33]. In a recent observational prospective study of 805 hypogonadal men, Saad
14 et al. reported that long-term treatment with testosterone undecanoate injections alleviated
15 erectile dysfunction and reduced the risk of major adverse cardiovascular events, prostate
16 cancer, and mortality³⁰.

17

18 **3.3 Patients treated for ADAM do not develop more prostate cancer than untreated men.**

19 A recent study using the UK clinical practice research datalink including 12,779 men
20 with late-onset hypogonadism reported that the use of TRT was not associated with an overall
21 increased risk of prostate cancer compared with nonuse³¹. A, randomized, double-blind
22 controlled study including 44 hypogonadal men treated with intramuscular injection of
23 testosterone (150 mg) or placebo every 2 weeks for 6 months showed no significant change in
24 prostate tissue levels of testosterone or DHT in the treated groups, despite normalization of their
25 serum testosterone levels²⁹. Analysis of the data extracted from the multi-national Registry of

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

8 According to the Surveillance, Epidemiology, and End Results-Medicare (SEER) data,
9 2,237 (1.5%) of 149,354 patients diagnosed with prostate cancer from 1992 to 2007 were under
10 androgen therapy at diagnosis³⁴. These patients' diseases were less often high grade or locally
11 advanced than those of men without testosterone replacement therapy (TRT) ³⁴. Moreover, no
12 significant difference in either overall or cancer-specific survivals was found between these two
13 groups of patients. However, men treated by TRT have more medical care and more PCa
14 screening tests than untreated men. Maybe because of this potential measurement bias, two
15 studies have shown a statistically significant reduction in the risk of prostate cancer mortality
16 (relative risk = 0.80; confidence interval 95%, 0.65 to 0.98) in patients treated with TRT ^{34, 35}.

17 Finally, in response to widespread concerns about the treatment with exogenous
18 testosterone for male hypogonadism, an international conference of consensus of experts was
19 convened³⁶. Nine resolutions were debated, with unanimous approval that the evidence doesn't
20 allow demonstrating an increased risk of PCa with exogenous testosterone treatment.

21

22 **4. Patients with localized prostate cancer may benefit from androgen therapy without** 23 **compromising their chance of curing cancer**

24 **4.1 Patients treated for localized PCa and androgen therapy**

1 Retrospective series focused on monitoring the possible biochemical recurrence after
2 radical prostatectomy on a population treated with androgens for ADAM found no or very few
3 recurrences even after 12 years of follow-up³⁷⁻⁴⁵ (Table 1). The same observation was made
4 in patients who received curative treatment with brachytherapy or external beam radiotherapy
5 (Table 1)^{38, 46-49}.

6

7 **4.2 PCa patients on active surveillance and androgen therapy**

8 This situation is increasingly common for low-risk prostate cancer. Active surveillance reports
9 third stop after one year of monitoring for histological progression and / or PSA [51]. Only few
10 studies have analyzed the PCa progression after testosterone replacement therapy: two observed
11 no clinical progression [47] whereas the other ones found between 8 and 15 % of patients with
12 increase in Gleason score⁵⁰⁻⁵³ (Table 2).

13

14 **5. Recommendations for androgen therapy**

15 Currently, no definitive recommendation has been made for the administration of androgen
16 therapy to patients with prostate cancer⁵⁴.

17 **5.1. Existing recommendations that concern prostate cancer risk are:**

18 *5.1.1. Recommendations of the American Endocrine Society (2018) at the initiation of androgen*
19 *therapy and during the treatment*⁵⁵

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

1 consultation.

2

3 *5.1.2 Recommendations of the International Society of Andrology; International Society for*
4 *the Study of Aging Male; European Association of Urology; European Academy of*
5 *Andrology; American Society of Andrology for androgen therapy of patients with localized*
6 *prostate cancer*⁵⁶ .

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

14 *5.1.3 Recommendations of the European Academy of Andrology (2020)*⁵⁷

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

20

21 **5.2 Pragmatical proposals for androgen therapy** (*authors' own recommendations based on*
22 *the current systematic review*):

23 *In the absence of prostate cancer*, the recommendations from the American Endocrine Society

24 [56] must be followed.

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

4 This treatment may be initiated for non-high-risk localized prostate cancer (Gleason score < 8,
5 pT1-2, preoperative PSA < 10ng/mL) hypogonadal patient at different time depending on the
6 PCa treatment. For low-risk localized PCa patients (Gleason score < 7, pT1-2, preoperative
7 PSA < 10ng/mL) on active surveillance, TRT could directly be proposed and followed as long
8 as the patient still meet the active surveillance criteria. After RP, postoperative PSA level
9 should be undetectable in order to initiate TRT. The European Association of Urology (EAU)
10 recommends starting TRT the first year after surgery⁵⁸. In case of brachytherapy, TRT should
11 be started after the PSA nadir is reached. The problem is more complex after external
12 radiotherapy, because there is still prostate tissue and serum PSA level does not reach its nadir
13 immediately. For this reason, the proposal of treatment with exogenous testosterone should be
14 made when the level of serum PSA is under 1 ng / mL⁵⁶.

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

19 Conclusion

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

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

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

13

14

1 **References**

2

3

4 1. Huggins, C., Hodges, C. V.: **Studies on Prostatic Cancer. I. The Effect of Castration,**
5 **of Estrogen and Androgen Injection on Serum Phosphatases in Metastatic**
6 **Carcinoma of the Prostate.** CA Cancer J Clin, 22: 232, 1972

7

8 2. Fowler, J. E., Jr., Whitmore, W. F., Jr.: **The Response of Metastatic Adenocarcinoma**
9 **of the Prostate to Exogenous Testosterone.** J Urol, 126: 372, 1981

10

11 3. Morgentaler, A., Traish, A. M.: **Shifting the Paradigm of Testosterone and Prostate**
12 **Cancer: The Saturation Model and the Limits of Androgen-Dependent Growth.**
13 Eur Urol, 55: 310, 2009

14

15 4. McFarland, J., Craig, W., Clarke, N. J. et al.: **Serum Testosterone Concentrations**
16 **Remain Stable between Injections in Patients Receiving Subcutaneous**
17 **Testosterone.** J Endocr Soc, 1: 1095, 2017

18

19 5. Staerman, F., Leon, P.: **Andropause (Androgen Deficiency of the Aging Male):**
20 **Diagnosis and Management.** Minerva Med, 103: 333, 2012

21

22 6. Gooren, L.: **Diagnosing Hypogonadism and Treating Decisions in Different Parts**
23 **of the World: Shifts in Patterns between 2006 and 2015.** Aging Male, 19: 46, 2016

24

25 7. Marks, L. S., Andriole, G. L., Fitzpatrick, J. M. et al.: **The Interpretation of Serum**
26 **Prostate Specific Antigen in Men Receiving 5alpha-Reductase Inhibitors: A**
27 **Review and Clinical Recommendations.** J Urol, 176: 868, 2006

28

29 8. Canby-Hagino, E., Hernandez, J., Brand, T. C. et al.: **Looking Back at Pcpt: Looking**
30 **Forward to New Paradigms in Prostate Cancer Screening and Prevention.** Eur
31 Urol, 51: 27, 2007

32

33 9. Muller, R. L., Gerber, L., Moreira, D. M. et al.: **Serum Testosterone and**
34 **Dihydrotestosterone and Prostate Cancer Risk in the Placebo Arm of the**
35 **Reduction by Dutasteride of Prostate Cancer Events Trial.** Eur Urol, 62: 757, 2012

36

37 10. Grober, E. D., Lamb, D. J., Khera, M. et al.: **Correlation between Simultaneous Psa**
38 **and Serum Testosterone Concentrations among Eugonadal, Untreated**
39 **Hypogonadal and Hypogonadal Men Receiving Testosterone Replacement**
40 **Therapy.** Int J Impot Res, 20: 561, 2008

41

- 1 11. Nair, K. S., Rizza, R. A., O'Brien, P. et al.: **Dhea in Elderly Women and Dhea or**
2 **Testosterone in Elderly Men.** N Engl J Med, 355: 1647, 2006
3
- 4 12. Algarte-Genin, M., Cussenot, O., Costa, P.: **Prevention of Prostate Cancer by**
5 **Androgens: Experimental Paradox or Clinical Reality.** Eur Urol, 46: 285, 2004
6
- 7 13. Mohr, B. A., Feldman, H. A., Kalish, L. A. et al.: **Are Serum Hormones Associated**
8 **with the Risk of Prostate Cancer? Prospective Results from the Massachusetts**
9 **Male Aging Study.** Urology, 57: 930, 2001
10
- 11 14. Morgentaler, A., Rhoden, E. L.: **Prevalence of Prostate Cancer among Hypogonadal**
12 **Men with Prostate-Specific Antigen Levels of 4.0 Ng/ml or Less.** Urology, 68: 1263,
13 2006
14
- 15 15. Garcia-Cruz, E., Piqueras, M., Ribal, M. J. et al.: **Low Testosterone Level Predicts**
16 **Prostate Cancer in Re-Biopsy in Patients with High Grade Prostatic Intraepithelial**
17 **Neoplasia.** BJU Int, 110: E199, 2012
18
- 19 16. Endogenous, H., Prostate Cancer Collaborative, G., Roddam, A. W. et al.: **Endogenous**
20 **Sex Hormones and Prostate Cancer: A Collaborative Analysis of 18 Prospective**
21 **Studies.** J Natl Cancer Inst, 100: 170, 2008
22
- 23 17. Garcia-Cruz, E., Piqueras, M., Huguet, J. et al.: **Low Testosterone Levels Are Related**
24 **to Poor Prognosis Factors in Men with Prostate Cancer Prior to Treatment.** BJU
25 Int, 110: E541, 2012
26
- 27 18. Albisinni, S., De Nunzio, C., Tubaro, A. et al.: **Greater Percent-Free Testosterone Is**
28 **Associated with High-Grade Prostate Cancer in Men Undergoing Prostate Biopsy.**
29 Urology, 80: 162, 2012
30
- 31 19. Loeb, S., Folkvaljon, Y., Damber, J. E. et al.: **Testosterone Replacement Therapy and**
32 **Risk of Favorable and Aggressive Prostate Cancer.** J Clin Oncol, 35: 1430, 2017
33
- 34 20. Massengill, J. C., Sun, L., Moul, J. W. et al.: **Pretreatment Total Testosterone Level**
35 **Predicts Pathological Stage in Patients with Localized Prostate Cancer Treated**
36 **with Radical Prostatectomy.** J Urol, 169: 1670, 2003
37
- 38 21. Salonia, A., Gallina, A., Briganti, A. et al.: **Preoperative Hypogonadism Is Not an**
39 **Independent Predictor of High-Risk Disease in Patients Undergoing Radical**
40 **Prostatectomy.** Cancer, 117: 3953, 2011
41
- 42 22. Porcaro, A. B., Monaco, C., Romano, M. et al.: **Investigative Clinical Study on**
43 **Prostate Cancer Part II: On the Role of the Pretreatment Total Psa to Free**

- 1 **Testosterone Ratio as a Marker Assessing Prostate Cancer Prognostic Groups**
2 **after Radical Retropubic Prostatectomy.** Urol Int, 85: 152, 2010
3
- 4 23. Neuzillet, Y., Raynaud, J. P., Dreyfus, J. F. et al.: **Aggressiveness of Localized**
5 **Prostate Cancer: The Key Value of Testosterone Deficiency Evaluated by Both**
6 **Total and Bioavailable Testosterone: Androcan Study Results.** Horm Cancer, 10:
7 36, 2019
8
- 9 24. Yamamoto, S., Yonese, J., Kawakami, S. et al.: **Preoperative Serum Testosterone**
10 **Level as an Independent Predictor of Treatment Failure Following Radical**
11 **Prostatectomy.** Eur Urol, 52: 696, 2007
12
- 13 25. Risbridger, G. P., Ball, E. M., Wang, H. et al.: **Re-Evaluation of Inhibin Alpha**
14 **Subunit as a Tumour Suppressor in Prostate Cancer.** Mol Cell Endocrinol, 225: 73,
15 2004
16
- 17 26. Dean, J. D., Carnegie, C., Rodzvilla, J. et al.: **Long-Term Effects of Testim(R) 1%**
18 **Testosterone Gel in Hypogonadal Men.** Rev Urol, 7: 87, 2005
19
- 20 27. Khera, M., Bhattacharya, R. K., Blick, G. et al.: **Changes in Prostate Specific Antigen**
21 **in Hypogonadal Men after 12 Months of Testosterone Replacement Therapy:**
22 **Support for the Prostate Saturation Theory.** J Urol, 186: 1005, 2011
23
- 24 28. Debruyne, F. M., Behre, H. M., Roehrborn, C. G. et al.: **Testosterone Treatment Is**
25 **Not Associated with Increased Risk of Prostate Cancer or Worsening of Lower**
26 **Urinary Tract Symptoms: Prostate Health Outcomes in the Registry of**
27 **Hypogonadism in Men.** BJU Int, 119: 216, 2017
28
- 29 29. Marks, L. S., Mazer, N. A., Mostaghel, E. et al.: **Effect of Testosterone Replacement**
30 **Therapy on Prostate Tissue in Men with Late-Onset Hypogonadism: A**
31 **Randomized Controlled Trial.** JAMA, 296: 2351, 2006
32
- 33 30. Saad, F., Caliber, M., Doros, G. et al.: **Long-Term Treatment with Testosterone**
34 **Undecanoate Injections in Men with Hypogonadism Alleviates Erectile**
35 **Dysfunction and Reduces Risk of Major Adverse Cardiovascular Events, Prostate**
36 **Cancer, and Mortality.** Aging Male: 1, 2019
37
- 38 31. Santella, C., Renoux, C., Yin, H. et al.: **Testosterone Replacement Therapy and the**
39 **Risk of Prostate Cancer in Men with Late-Onset Hypogonadism.** Am J Epidemiol,
40 188: 1666, 2019
41
- 42 32. Shabsigh, R., Crawford, E. D., Nehra, A. et al.: **Testosterone Therapy in**
43 **Hypogonadal Men and Potential Prostate Cancer Risk: A Systematic Review.** Int J
44 Impot Res, 21: 9, 2009

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5
6
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11
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13
14
15
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17
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24
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27
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31
32
33
34
35
36
37
38
39
40
41
42

33. Calof, O. M., Singh, A. B., Lee, M. L. et al.: **Adverse Events Associated with Testosterone Replacement in Middle-Aged and Older Men: A Meta-Analysis of Randomized, Placebo-Controlled Trials.** J Gerontol A Biol Sci Med Sci, 60: 1451, 2005

34. Kaplan, A. L., Hu, J. C.: **Use of Testosterone Replacement Therapy in the United States and Its Effect on Subsequent Prostate Cancer Outcomes.** Urology, 82: 321, 2013

35. Schroder, F. H., Hugosson, J., Roobol, M. J. et al.: **Screening and Prostate-Cancer Mortality in a Randomized European Study.** N Engl J Med, 360: 1320, 2009

36. Morgentaler, A., Zitzmann, M., Traish, A. M. et al.: **Fundamental Concepts Regarding Testosterone Deficiency and Treatment: International Expert Consensus Resolutions.** Mayo Clin Proc, 91: 881, 2016

37. Agarwal, P. K., Oefelein, M. G.: **Testosterone Replacement Therapy after Primary Treatment for Prostate Cancer.** J Urol, 173: 533, 2005

38. Davila HH, A. C., Hall MK, Salup Raoul, Lockhart JL, Carrion RE.: **Analysis of the Psa Response after Testosterone Supplementation in Patients Who Previously Received Management for Their Localized Prostate Cancer [Abstract].** Journal of Urology 179 2008

39. Isbarn, H., Pinthus, J. H., Marks, L. S. et al.: **Testosterone and Prostate Cancer: Revisiting Old Paradigms.** Eur Urol, 56: 48, 2009

40. Kaufman, J. M., Graydon, R. J.: **Androgen Replacement after Curative Radical Prostatectomy for Prostate Cancer in Hypogonadal Men.** J Urol, 172: 920, 2004

41. Khera, M., Grober, E. D., Najari, B. et al.: **Testosterone Replacement Therapy Following Radical Prostatectomy.** J Sex Med, 6: 1165, 2009

42. Matsushita K, K. D., Stember DS et al.: **Analysis of the Safety and Efficacy of Testosterone Supplementation Following Radical Prostatectomy.** J Sex Med 2012;9, 2012

43. Nabulsi O, T. R., Gotto G et al. : **Outcomes Analysis of Testosterone Supplementation in Hypogonadal Men Following Radical Prostatectomy.** Journal of Urology 179, 2008

- 1 44. Pastuszak, A. W., Pearlman, A. M., Lai, W. S. et al.: **Testosterone Replacement**
2 **Therapy in Patients with Prostate Cancer after Radical Prostatectomy.** J Urol, 190:
3 639, 2013
4
- 5 45. Sathyamoorthy K, S. M., Mohammed O et al: **Testosterone Replacement Therapy in**
6 **High Risk Patients Following Radical Prostatectomy [Abstract 1498].** Journal of
7 Urology 183 2010
8
- 9 46. Morales, A., Black, A. M., Emerson, L. E.: **Testosterone Administration to Men with**
10 **Testosterone Deficiency Syndrome after External Beam Radiotherapy for**
11 **Localized Prostate Cancer: Preliminary Observations.** BJU Int, 103: 62, 2009
12
- 13 47. Ory, J., Flannigan, R., Lundeen, C. et al.: **Testosterone Therapy in Patients with**
14 **Treated and Untreated Prostate Cancer: Impact on Oncologic Outcomes.** J Urol,
15 196: 1082, 2016
16
- 17 48. Pastuszak, A. W., Pearlman, A. M., Godoy, G. et al.: **Testosterone Replacement**
18 **Therapy in the Setting of Prostate Cancer Treated with Radiation.** Int J Impot Res,
19 25: 24, 2013
20
- 21 49. Sarosdy, M. F.: **Testosterone Replacement for Hypogonadism after Treatment of**
22 **Early Prostate Cancer with Brachytherapy.** Cancer, 109: 536, 2007
23
- 24 50. Hashimoto, T., Rahul, K., Takeda, T. et al.: **Prostate Magnetic Resonance Imaging**
25 **Findings in Patients Treated for Testosterone Deficiency While on Active**
26 **Surveillance for Low-Risk Prostate Cancer.** Urol Oncol, 34: 530 e9, 2016
27
- 28 51. Kacker, R., Hult, M., San Francisco, I. F. et al.: **Can Testosterone Therapy Be Offered**
29 **to Men on Active Surveillance for Prostate Cancer? Preliminary Results.** Asian J
30 Androl, 18: 16, 2016
31
- 32 52. Lawrence C. Jenkins, R. K., Boback M. Berookhim, Jonathan Coleman, James A.
33 Eastham, BehfarEhdaie, Vincent P. Laudone, Christian J. Nelson, John P. Mulhall:
34 **Safety of Testosterone Therapy in Patients on Active Surveillance for Prostate**
35 **Cancer.** J Urol, 195, 2016
36
- 37 53. Morgentaler, A., Lipshultz, L. I., Bennett, R. et al.: **Testosterone Therapy in Men with**
38 **Untreated Prostate Cancer.** J Urol, 185: 1256, 2011
39
- 40 54. Kwong, J. C. C., Krakowsky, Y., Grober, E.: **Testosterone Deficiency: A Review and**
41 **Comparison of Current Guidelines.** J Sex Med, 16: 812, 2019
42

- 1 55. Bhasin, S., Brito, J. P., Cunningham, G. R. et al.: **Testosterone Therapy in Men with**
2 **Hypogonadism: An Endocrine Society Clinical Practice Guideline.** J Clin
3 Endocrinol Metab, 103: 1715, 2018
4
- 5 56. Wang, C., Nieschlag, E., Swerdloff, R. et al.: **Investigation, Treatment and**
6 **Monitoring of Late-Onset Hypogonadism in Males: Isa, Issam, Eau, Eaa and Asa**
7 **Recommendations.** Eur J Endocrinol, 159: 507, 2008
8
- 9 57. Corona, G., Goulis, D. G., Huhtaniemi, I. et al.: **European Academy of Andrology**
10 **(Eaa) Guidelines on Investigation, Treatment and Monitoring of Functional**
11 **Hypogonadism in Males.** Andrology, 2020
12
- 13 58. Jungwirth, A., Giwercman, A., Tournaye, H. et al.: **European Association of Urology**
14 **Guidelines on Male Infertility: The 2012 Update.** Eur Urol, 62: 324, 2012
15
16

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) Gleason 7 (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

^aMedian (interquartile range)

^bmean (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

^aMedian (interquartile range)

^bmean ± 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	<ul style="list-style-type: none"> • TRT contraindicated in men with untreated prostate cancer • Men > 40 : PSA + DRE before TRT
2018	American Endocrine Society	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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****	<ul style="list-style-type: none"> • <i>In the absence of prostate cancer:</i> <ul style="list-style-type: none"> ⇒ AES (2018) recommendations should be followed • <i>Known prostate cancer with:</i> <ul style="list-style-type: none"> ○ High risk localized disease ○ Positive surgical margins ○ Positive lymph node ○ Metastatic disease <ul style="list-style-type: none"> ⇒ Patient should not be treated with TRT • <i>Non-high risk localized prostate cancer** after treatment</i> <ul style="list-style-type: none"> ⇒ TRT might be initiated: <ul style="list-style-type: none"> ○ After RP, if PSA is undetectable ○ After Brachytherapy, after the PSA nadir is reached ○ After Radiotherapy, if PSA < 1 ng/ml • <i>Low risk localized prostate cancer*** with Active surveillance</i> <ul style="list-style-type: none"> ⇒ 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