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REVIEW ARTICLE

Clinical evaluation and treatment in men with low testosterone levels and prostate cancer*

B.M. Ljubetic, F. Parada, J.M. Flores*

Male Sexual and Reproductive Medicine Program, Memorial Sloan-Kettering Cancer Center, New York City, New York, USA

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Abstract

Introduction: A high prevalence of low testosterone levels has been reported in men with prostate cancer. The use of testosterone therapy in men with a history of prostate cancer is still controversial, and there is uncertainty regarding the management of these patients.

Methods: We analyzed the European and American guidelines on this topic and presented the clinical experience in the management of patients with low testosterone levels and a history of prostate cancer in one of the world's leading cancer centers.

Results: According to the published evidence to date, testosterone therapy in men with prostate cancer does not increase the risk of prostate cancer recurrence in the short and medium term, but there is a lack of data on the long term. Symptomatic men with low testosterone levels who are candidates for this therapy need a thorough clinical evaluation before commencing testosterone therapy. Evaluation of prostate cancer history including type of treatment administered, pathologic stage of prostate cancer and prostate specific antigen should be requested before and during testosterone treatment to assess its trend.

Conclusion: Prostate-specific antigen should remain undetectable after radical prostatectomy or stable after radiotherapy. Otherwise, it would be a sign of uncontrolled prostate cancer, and the patient may require cessation of testosterone therapy and referral to oncology for further evaluation.

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* Corresponding author.
E-mail address: floresmj@mskcc.org (J.M. Flores).

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PALABRAS CLAVE
Deficiencia de testosterona;
Testosterona Baja;
Terapia de testosterona;
Cáncer de próstata

Evaluacion clinica y tratamiento en hombres con testosterona baja y cancer de prostata

Resumen

Introducción: En hombres con cáncer de próstata, se ha reportado una alta prevalencia de niveles bajos de testosterona. El tratamiento con testosterona en hombres con antecedentes de cáncer de próstata sigue siendo controversial y existe incertidumbre como manejar estos pacientes.

Métodos: Se realizo un análisis de las guías Europeas y Americanas en torno al tema y se presentó la experiencia clínica en el manejo de pacientes con testosterona baja y con historia de cáncer de próstata de un centro oncológico líder a nivel mundial.

Resultados: Actualmente, la evidencia publicada no ha demostrado que la terapia con testosterona en hombres con cáncer de próstata aumenta el riesgo de la recurrencia del cáncer de próstata a corto y mediano plazo, pero que existe una falta de evidencia en el largo plazo. Los hombres sintomáticos y con testosterona baja y son candidatos para recibir esta terapia requieren una completa evaluación clínica previo al inicio del tratamiento. La evaluación de la historia del cáncer de próstata incluye el tipo de tratamiento realizado, el estado patológico del cáncer de próstata y el antígeno prostático específico debe solicitarse antes del inicio de la terapia con testosterona, y seriadamente desde el inicio del tratamiento para evaluar su tendencia.

Conclusión: El antígeno prostático específico se debe mantener indetectable después de una prostatectomía radical o estable después de la radioterapia. En caso contrario, significa que el cáncer de próstata no está bajo control y el paciente podría requerir detener el tratamiento con testosterona y una evaluación adicional por oncología.

Introduction

According to the American Urological Association (AUA) guidelines for the Evaluation and Management of Testosterone Deficiency, testosterone deficiency (the term chosen by the Panel) is defined by two total testosterone levels drawn in an early morning fashion, less than 300 ng/dL (10.4 nmol/L).[1] In the Sexual and Reproductive Health Guidelines of the European Association of Urology (EAU), male hypogonadism (the Panel has agreed to use this term) is defined as two total testosterone samples taken before 11 AM less than 12 nmol/L (3.5 ng/mL).[2,3] The prevalence of low testosterone levels varies according to the definition used and the patient population being studied, and figures ranging between 2% and 50% have been reported in the literature.[1] The prevalence of low testosterone levels increases with age.[4] The Baltimore Longitudinal Study of Aging reported a prevalence of low testosterone of 12% in men aged 50 years and of 50% in men 80 years and older.[4–6] Low testosterone levels have been associated with worsened general health status and quality of life,[7,8] increased rates of cardiovascular events, lower bone mineral density, and increased difficulty in achieving glycemic control in men with diabetes.[2]

A high prevalence of low testosterone levels has been reported among men with prostate cancer.[9,10] Recently published data reported prevalence rates reaching 30% of low testosterone levels, defined as levels less than 300 ng/dL (10.4 nmol/L), in men with prostate cancer.[11] In this same study, a Gleason score greater than or equal to 8, and a prostate antigen less than 4 ng/mL, were significant predictors of low testosterone in men with prostate cancer.[11] Another study compared testosterone levels in men with prostate cancer vs. men with benign prostatic hyperplasia and reported that mean testosterone levels were significantly lower in prostate cancer patients compared to the control group, 330 ng/dL (11. 4 nmol/L) vs. 440 ng/dL (15.3 nmol/L), respectively. Additionally, the percentage of men with low testosterone levels, defined as levels less than 240 ng/dL (8.3 nmol/L), was significantly higher in men with prostate cancer (32%) compared to men with benign prostatic hyperplasia (10%).[12]

In the 1940s, Nobel laureate Charles Huggins demonstrated that the course of prostate cancer could be affected by androgen deprivation. The legacy of his work established the dogma that testosterone was essential for the development of prostate cancer. Since the introduction of topical testosterone formulations in the 1990s, the belief that testosterone levels correlate linearly with prostate cancer has shifted; current evidence has demonstrated a complex biochemical relationship between testosterone and prostate cancer.[11] Although a more complete understanding of the role of testosterone in prostate cancer oncogenesis has been gained since Huggins' era, there are still doubts concerning this relationship. This is illustrated by the fact that since 2015, the Food and Drug Administration (FDA) required all testosterone products to include the warning that patients treated with testosterone could be at increased risk for prostate cancer, and that its use was contraindicated in men with prostate cancer.[13] This regulatory act raised uncertainty among patients and many physicians regarding the safety of testosterone therapy in men with prostate cancer. To date, the European Medicines Agency (EMA) does not indicate a warning regarding testosterone-containing medicines and the risk of prostate cancer, and states that there is no consistent evidence.[14]

The guidelines of the European Academy of Andrology establish that testosterone treatment is contraindicated in men with locally advanced or metastatic prostate cancer.[15] Furthermore, they state that evidence on the safety of testosterone use in men with a history of prostate cancer has is scarce, so it should be discussed with the patient and limited to low-risk individuals.[15] According to the European guidelines, men with low testosterone who have been surgically treated for localized prostate cancer and who remain with PSA level <0.01 ng/mL after at least one year follow-up may be considered for testosterone therapy; the Panel emphasizes on

the risks and benefits and lack of sufficient safety data on long term follow-up.[3] In contrast, the AUA guidelines for men with testosterone deficiency and prostate cancer state that it should be a shared decision between the physician and patient, and that patients should be informed of the risks and benefits of testosterone therapy. According to this Panel, therapy may be considered in patients with a favorable surgical specimen pathology (negative margins, uninvolved seminal vesicles, and negative lymph nodes) and undetectable prostate-specific antigen.[1] However, there is still uncertainty regarding the safe and reliable management of patients with prostate cancer and low testosterone levels, and guidelines on the treatment of these patients are still needed.

Testosterone therapy: evaluation prior to initiation of treatment

Symptomatic men with low testosterone levels who meet the criteria for testosterone deficiency and are candidates for this therapy require proper clinical evaluation prior to initiation of treatment. The AUA guidelines, published in 2018, recommend assessing the following parameters in these patients: (i) presence of gynecomastia, (ii) interest in preserving fertility, (iii) baseline hematocrit, (iv) and PSA level in men over 40 years of age.[1] The EAU guidelines recommend, prior to testosterone therapy initiation, to rule out the use of drugs or substances that may interfere with testosterone production or action, to evaluate the presence of obesity, metabolic syndrome, diabetes, and to examine the existence of contraindications for testosterone therapy. According to these guidelines, breast cancer, locally advanced or metastatic prostate cancer, desire to preserve fertility, baseline hematocrit $\geq$54%, and uncontrolled or poorly controlled congestive heart failure are absolute contraindications for T therapy. An IPSS score >19, baseline hematocrit between 48 and 50%, and familial history of venous thromboembolism constitute relative contraindications.[3] In our clinical practice, patients who meet low testosterone criteria and are candidates for testosterone therapy undergo systematical evaluation of different clinical variables prior to initiation of testosterone therapy, in order to ensure consistent and adequate assessment of these patients and to identify critical points that should be managed prior to initiation of testosterone therapy.[16] Table 1 summarizes the list of clinical parameters used for clinical evaluation prior to commencement of testosterone therapy.

Prostate cancer and baseline PSA

It is paramount to identify the right patient with prostate cancer who will safely benefit from therapy. In our clinical practice, men with low testosterone levels undergo an evaluation of prostate cancer history that includes several items. These include the type of treatment received, the date of treatment, and pathology reports of the biopsy or surgical specimen, including Gleason score, Gleason group, presence of extracapsular invasion, positive margins, positive lymph nodes, and seminal vesicle involvement, in order to determine the pathologic stage of the prostate cancer (localized vs. locally advanced/metastatic). Prostate-specific antigen level is requested prior to the initiation of testosterone therapy, and all controls include PSA measurements from the initiation of treatment to assess their trend. PSA should remain undetectable after radical prostatectomy or stable and at minimal values after radiotherapy. Otherwise, it means that the prostate cancer is not controlled and the patient requires referral to oncology for further evaluation. It is important to know that there is a period of time between radiotherapy and initiation of testosterone therapy to allow for (1) recovery of testosterone after treatment, and (2) radiation effects for up to 1 year in prostate tissue after treatment.[1] Additionally, in our clinical practice, patients are informed about the published data on the potential occurrence of biochemical recurrence at short- and medium-term follow-up, emphasizing that current evidence has not shown that testosterone therapy increases the risk of prostate cancer recurrence in men with prostate cancer in the short- and medium-term, but that there is a lack of evidence in the long term.

Testosterone and PSA levels in the follow-up of prostate cancer patients

In our clinical practice, the initial workup of men with prostate cancer and low testosterone levels includes total testosterone, measured (not calculated) free testosterone, luteinizing hormone, sex hormone binding globulin, estradiol, bone densitometry, prostate-specific antigen, and hematocrit. The PSA curve is critical in men with post-therapy prostate cancer: it must be undetectable in men who have undergone radical prostatectomy and stable in men after radiotherapy to be considered eligible for testosterone therapy. For men who were treated with radiation therapy, testosterone therapy is generally initiated 2 years after treatment. After testosterone therapy is started, testosterone levels should be monitored every 4 weeks until stable therapeutic levels are reached. During follow-up, testosterone panels should include total testosterone, free testosterone, luteinizing hormone, sex hormone-binding globulin, estradiol, prostate-specific antigen, and hemogram (hematocrit). When testosterone levels achieve therapeutic range (400—600 ng/dL, 13.9—20.8 nmol/L) accompanied by symptom/sign improvement, the AUA guidelines[1] recommend evaluation every 6 months.[1,3] In patients who reach therapeutic levels but fail to achieve symptom or sign improvement up to six months after commencement of treatment, cessation of testosterone therapy should be discussed.[1] If therapeutic levels are not achieved, adjustment or change in the modality of testosterone therapy should be considered. The EAU guidelines suggest that the first evaluation should be planned after 3 months of treatment, and further evaluation could be scheduled at 6 or 12 months, according to patient characteristics and biochemical testing results. Patients with elevated hematocrit should be evaluated every 3 months during the first year and every 6 months thereafter. This Panel also recommends maintaining a testosterone range similar to the physiologic range (280—873 ng/dL, 9.6—30 nmol/L). Prostate antigen assessment should be mandatory before and during testosterone therapy. In the first year, at 3, 6 and 12 months, and annually in subsequent years. These guidelines also indicate that the decision to stop testosterone therapy or to perform a prostate biopsy due to elevated PSA or altered digital rectal examination should be based on the

Table 1 List of clinical parameters to assess before commencing testosterone therapy.

Parameter	Question
Baseline PSA level	Baseline PSA (Yes/No, value) Digital rectal examination (normal/altered) History of prostate cancer (Yes/No) Family history of prostate cancer (Yes/No)
Baseline hematocrit level	Hematocrit level ≥45% (Yes/No, value)
History of Obstructive Sleep Apnea	Obstructive Sleep Apnea (Yes/No, date) Risk evaluation for Obstructive sleep apnea (STOPBANG score) Assessment of treatment adherence in men with obstructive sleep apnea (Yes/No)
Topical testosterone transference risk	Assess the risk of transference to children under 12 years old (low: in occasional contact with them, less than once a month/high: in contact once a month or more)
Interest in fertility	Interest in fertility (Yes/No)
Baseline luteinizing hormone levels	High luteinizing hormone levels (Yes/No, value)
Prolactin levels	High prolactin levels (Yes/No, value)
Use of anti-coagulants	Use of anti-coagulants (Yes/No)
Risk of venous thromboembolism	History of venous thromboembolism and/or pulmonary embolism (Yes/No, date)
History of cardiovascular events	Acute myocardial infarction (Yes/No, date) Cerebrovascular accident (Yes/No, date) Congestive heart failure (Yes/No, date)
Breast symptoms	Breast symptoms (Yes/No) Gynecomastia (Yes/No) History of breast cancer (Yes/No)

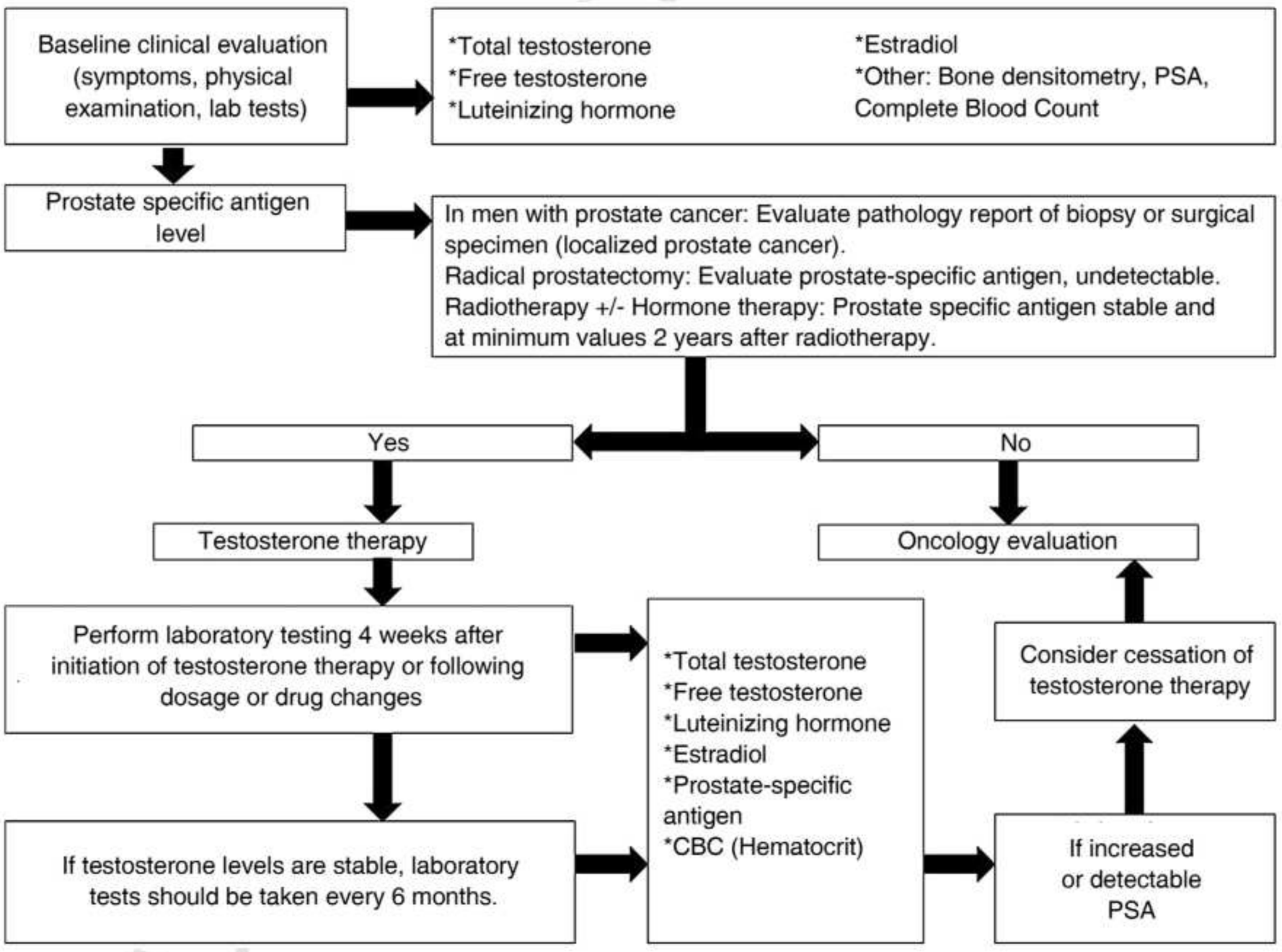

Figure 1 Clinical algorithm for the management of men with prostate cancer and testosterone therapy.

Table 2 Recommendations of the AUA and EAU guidelines for the management of low testosterone in men with prostate cancer.

	AUA[1]	EAU[3]
Requested test	Two total testosterone measurements taken on separate occasions in an early morning fashion.	Two measurements of total testosterone before 11am
Definition of low testosterone	<300 ng/dL (10.4 nmol/L)	<346 ng/dL (12 nmol/L).
Recommended testosterone therapeutic levels	450–600 ng/dL (13.9–20.8 nmol/L)	280–873 ng/dL (9.6–30 nmol/L)
Prostate cancer	[•]Shared decision • Patients should be informed about risks and benefits. • Post-radical prostatectomy: Testosterone therapy can be considered in men who have undergone radical prostatectomy with favorable pathology (e.g., negative margins, negative seminal vesicles, negative lymph nodes), and who have undetectable PSA postoperatively. • Post-radiotherapy: TT could be considered after RT in patients with a steady decline in PSA values to <0.1 ng/mL or with nonsignificant changes in PSA, with no signs of recurrence or progression of prostate cancer.	[•]There is lack of data on the safety of testosterone therapy; especially on the long-term • Testosterone therapy is contraindicated in men with locally advanced or metastatic prostate cancer. • Men who have been surgically treated for localized (low risk) prostate cancer, who remain with undetectable PSA levels for 1 year, and who present low testosterone symptoms may be considered for testosterone therapy. • Counseling on the benefits and lack of sufficient safety data on long term follow-up.

recommendations of the EAU prostate cancer guidelines.[3] In our clinical practice, we closely monitor PSA levels on every testosterone panel, if PSA level is detectable in a patient with a history of radical prostatectomy, or increasing compared to baseline levels in men who underwent radiation therapy, cessation of testosterone therapy should be considered, and the patient should be referred to oncology for further study and possibly adjuvant treatment. Fig. 1 summarizes the clinical algorithm for men with prostate cancer and testosterone therapy. Table 2 compares the recommendations of the AUA and EAU guidelines for the management of low testosterone levels in men with prostate cancer.

Conclusion

In our clinical practice, we believe that patients with a history of prostate cancer need a thorough evaluation and require extensive counseling on risks and benefits. To date, published evidence on prostate cancer patients has not shown that testosterone therapy is associated with an increased risk of prostate cancer recurrence in the short and medium term, but there is a lack of evidence in the long term. Men with low testosterone levels combined with symptoms who meet the criteria for testosterone deficiency and are candidates for this therapy require adequate and comprehensive clinical evaluation prior to initiation of treatment. This is important to select those prostate cancer patients who will safely benefit from treatment. In men with a history of prostate cancer, evaluation of (i) the type of treatment performed, (ii) determination of the pathologic stage of prostate cancer and (iii) the baseline PSA and its trend prior to initiation of testosterone therapy is mandatory. Based on PSA, patients would be candidates for initiation of testosterone therapy if PSA levels remain undetectable after radical prostate surgery or stable and at minimal values after radiotherapy. Subsequent PSA monitoring after initiation of testosterone therapy is imperative. PSA should remain undetectable after radical prostate surgery or stable after radiotherapy. Otherwise, it means that prostate cancer is not controlled, and the patient would require cessation of testosterone therapy and referral to oncology for further evaluation.

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Conflicts of interest

The authors declare that they have no conflicts of interest. Q3

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