Advanced Prostate Adenocarcinoma and Androgen Deprivation Therapy. Clinical Outcomes, Risk Stratification, and Therapeutic Results

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Preface

Scientific and clinical knowledge often advances through large-scale trials, meta-analyses, and consensus guidelines. Yet there remains a distinct and enduring value in studies grounded in the realities of specific institutions, where disease, patients, and therapeutic decisions acquire a tangible human dimension. This volume emerges from that space — the intersection between clinical observation, institutional practice, and reflective analysis.

Prostate cancer continues to represent one of the most significant oncological challenges in men worldwide. Its biological diversity, variable clinical course, and evolving therapeutic landscape demand not only technical expertise but also interpretative judgment. Within advanced stages of the disease, where curative options are limited, treatment strategies are frequently shaped by a delicate balance between survival, symptom control, and quality of life.

This work presents a structured characterization of patients diagnosed with advanced prostate adenocarcinoma managed through total androgen deprivation therapy in a Cuban tertiary hospital. Beyond reporting clinical data, the study invites readers to consider broader questions: how therapeutic decisions are contextualized, how biomarkers are interpreted, and how treatment effects are experienced by patients.

The chapters that follow combine theoretical foundations, methodological clarity, and clinical interpretation. Together, they offer an integrated perspective that may serve clinicians, residents, researchers, and healthcare professionals interested in urologic oncology and therapeutic outcomes in real-world settings.

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Introduction

Prostate cancer occupies a central position in contemporary urologic oncology. Its global incidence, strong association with aging, and heterogeneous clinical behavior have transformed it into a persistent concern for healthcare systems across regions with markedly different demographic and economic profiles.

While early detection strategies and biomarker-driven diagnostics have reshaped the clinical landscape, a substantial proportion of patients continue to present with locally advanced or metastatic disease. In these scenarios, therapeutic objectives inevitably shift. The emphasis moves from eradication of disease toward containment, stabilization, and preservation of functional well-being.

Androgen deprivation therapy remains the cornerstone of management in advanced prostate cancer. Its historical origins trace back to the seminal observations of hormonal dependence in prostatic tumors, which established a paradigm still relevant decades later. Despite significant advances in systemic treatments, hormonal manipulation continues to define the backbone of therapeutic intervention in this stage.

The clinical application of total androgen deprivation raises multiple considerations. Its effects extend beyond tumor biology, influencing metabolic regulation, bone health, cardiovascular status, and sexual function. Treatment outcomes therefore cannot be evaluated solely through biochemical or radiological parameters; they must also account for the lived experience of patients.

This volume develops an institutional analysis of advanced prostate adenocarcinoma treated with total androgen deprivation between 2017 and 2020. The discussion integrates epidemiological context, molecular and histopathological features, diagnostic reasoning, therapeutic strategies, and clinical outcomes. Through this framework, the book seeks to contribute to a nuanced understanding of disease behavior and therapeutic response within a defined clinical environment.

Abstract

Advanced prostate adenocarcinoma represents a complex clinical entity characterized by biological heterogeneity, variable progression patterns, and evolving therapeutic challenges. Although early detection initiatives have modified diagnostic trends, a considerable number of patients continue to present with advanced disease, where management priorities shift toward disease control, symptom mitigation, and quality-of-life preservation.

This book offers a comprehensive examination of advanced prostate adenocarcinoma managed with total androgen deprivation therapy within a tertiary-care hospital setting. The analysis is grounded in an observational, descriptive, cross-sectional study of patients treated between 2017 and 2020. Emphasis is placed on risk stratification at diagnosis, patterns of biochemical response, detection of disease progression, and interpretation of key biomarkers, including prostate-specific antigen and serum testosterone levels.

Beyond clinical metrics, the text addresses the multidimensional consequences of androgen deprivation, particularly its impact on sexual function and general health status. The discussion situates therapeutic outcomes within the broader context of endocrine regulation, tumor biology, and institutional clinical practice.

By integrating theoretical foundations, methodological structure, and clinical interpretation, this volume contributes an institution-based perspective on treatment response and disease behavior. The findings underscore the predominance of high- and very-high-risk presentations, the diagnostic relevance of biomarkers, and the need for individualized therapeutic monitoring.

The work is intended for clinicians, urology residents, oncology specialists, and researchers seeking an analytically grounded yet clinically oriented exploration of advanced prostate cancer management.

Keywords: Prostate cancer; Advanced prostate adenocarcinoma; Androgen deprivation therapy; Risk stratification; Prostate-specific antigen; Hormonal resistance.

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Chapter 01 / Capítulo 01

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Clinical Context and Problem Statement

Cancer has become a major health problem due to its high incidence and mortality rates, which have been increasing in recent years for various reasons, including increased life expectancy.

Prostate cancer affects older men more frequently than younger men do. Consequently, it is a greater health problem in developed countries, as they have a greater proportion of this age group, which affects mainly men over the age of 50.[1]

Since 1985, there has been a slight increase in the number of deaths from prostate cancer in most countries, even in countries or regions where it is not common, increasing the probability of developing this disease by 15 %, a risk that increases progressively with age, and the risk of dying from it by 3 %.[2]

In Europe, prostate cancer is the most common cancer, with an incidence of 214 cases per 1,000 men, surpassing that of lung and colorectal cancers.[3]

The highest incidence rates are found in Austria and North America (111,6 and 97,2 cases per 100 000 men, respectively). The lowest rates are reported in Asian countries (4,5—10,5 cases per 100 000 men).[4]

In South Africa and the Caribbean, mortality rates are highest in populations of African descent (19 to 24 deaths per 100 000 men).

In the United States in 2015, 220 800 new cases were diagnosed, and 27 540 people died from this cause in the same period, making it the second leading cause of death. It is estimated that 75 % of new cases are detected in people over 65 years of age, with an estimated 31 620 deaths from this disease this year.[5]

However, the death rate declined by more than half from the mid-1990s to the mid-2000s. From 2014–2018, the death rate remained stable. The survival of a particular person depends on the type of prostate cancer and the stage of the disease. There are more than 3,1 million prostate cancer survivors in the United States today.[6]

In Latin America, according to the World Health Organization's International Agency for Research on Cancer, it has an annual incidence of 54,2 %. Prostate cancer is the leading cause of death in Mexico, accounting for 21,4 % of all cancers, with an incidence of 27,3 per 100 000 men, causing 6 367 deaths in 2012, with a rate of 11,3 per 100 000 men.[7,8]

In Cuba, cancer is the second leading cause of death after cardiovascular disease in people over 50, and in men, malignant tumors of the airways are the leading cause of death. In 2017, prostate cancer was the leading cause of cancer death in men in Cuba, with a mortality rate of 55.7 per 100,000 inhabitants.[9]

Cuba's annual health statistics report that the mortality rate per 100 000 inhabitants in urban areas is 30,1 and that in rural areas is 25,2. One in ten patients may develop prostate cancer, and three in 100 may die from it. Symptoms may appear when the cancer is already very

advanced, requiring increasingly aggressive procedures that affect the patient's quality of life and life expectancy.[10]

When the disease presents, it is necessary to identify the hereditary risk factor, as this risk factor is 2–3 times greater in first-degree relatives. The most common type of prostate tumor is adenocarcinoma, and the role of mutations and changes observed in the function of various genes in its development has recently been revitalized. Most cases are located preferentially in the peripheral zone of the prostate gland (55 %-70 %) or in the transitional zone (25 %-50 %); this circumstance facilitates its eventual detection by digital rectal examination, since growth in the central zones of the gland is rare (<10 %).[11]

In patients with advanced prostate cancer, the available treatment options are very varied, and criteria such as quality of life and treatment tolerance, assuming therapeutic efficacy, have become increasingly important, as the average survival rate is approximately three years.

The therapeutic focus in these progressive forms of prostate disease is androgen deprivation, the basis for which was historically established by Huggings and Hodges in 1941 when they observed the androgen dependence of prostate cancer. Its palliative, although not curative, nature over the last 50 years allows us to emphasize its acceptance and therapeutic efficacy in this disease and its common complications, such as bone pain and obstructive uropathy.[12]

Problem and purpose of the study

Advanced prostate adenocarcinoma represents a sustained clinical challenge in contemporary urological practice. Its evolution, marked by considerable biological heterogeneity and variable clinical trajectories, requires therapeutic decisions that transcend strictly curative logic. In advanced stages, the approach is geared toward disease control, prolonging survival, and preserving quality of life.

Total androgen deprivation has been the fundamental therapeutic approach in this context for decades. Its biological basis, which is based on the hormonal dependence of prostate tumor tissue, has been widely documented. However, the clinical response to this strategy is not uniform. Progression times, the appearance of recurrences, the transition to hormone-resistant states, and variability in biomarker expression raise important questions for both clinical practice and the evaluation of therapeutic outcomes.

Within this framework, there is a need to examine the behavior of advanced prostate adenocarcinoma in specific healthcare contexts. Institutional dynamics, patient profiles, available diagnostic resources, and clinical follow-up regimens can significantly influence the observed evolution. Institutional analysis therefore allows for the identification of clinical patterns, evolutionary timelines, and operational challenges that are not always fully visible in multicenter studies or controlled trials.

The present study was conducted at the Joaquín Albarrán Domínguez Clinical Surgical Teaching Hospital, a leading institution in specialized urological care. This research aimed to characterize the behavior of advanced prostate adenocarcinoma in patients undergoing total androgen deprivation from 2017–2020. This time frame allowed for the examination of clinical evolution within a homogeneous therapeutic framework, considering relevant diagnostic, biochemical, and clinical variables.

The main purpose of the analysis was to understand how the response to total androgen deprivation manifests itself in terms of progression, recurrence, and early detection of tumor activity. Particular attention has been given to the dynamics of biomarkers, especially prostate-specific antigen (PSA), whose interpretation continues to be debated in advanced disease scenarios. The role of testosterone dosing as a complementary tool in identifying hormone resistance was also explored.

The evaluation of disease behavior is not limited to biochemical or tumor progression indicators. The patient's clinical experience, including the impact of treatment on sexual function and overall health, was a particularly relevant analytical dimension. In prolonged hormone therapies, side effects have a substantial effect on adherence, the perception of well-being, and quality of life.

From this perspective, the study integrated clinical, diagnostic, and functional objectives. This study sought to identify the time of recurrence after the start of treatment, analyze the usefulness of PSA in the early detection of signs of tumor activity, examine the sensitivity of testosterone dosing in cases of suspected hormone resistance, and characterize the impact of hormone treatment on the patient's sexual health and overall health.

Rather than offering definitive answers, the analysis aimed to construct a structured clinical interpretation of the phenomenon within the institutional context studied. The complexity of advanced prostate adenocarcinoma requires cautious interpretations, attention to individual variability and the inherent limitations of observational designs.

Justification of the Problem

Androgen deprivation therapy (ADT) is the cornerstone of treatment for advanced prostate cancer and has also been shown to play an important role in the treatment of high-risk localized cancer.

In recent years, in line with the increase in prostate cancer diagnosis owing to PSA testing, there has been a shift toward its increasing use in the early stages of the disease, either as primary treatment or as an adjunct to curative treatments such as radiotherapy.

In the socioeconomic context, it allows for adequate care and treatment of patients with advanced prostate adenocarcinoma, providing them with more personalized follow-up from the moment of diagnosis or with early detection of hormonal escape, in addition to the rational use of healthcare costs by optimizing the resources allocated to androgen deprivation therapy, reducing the use of complementary tests, and improving quality of life. From an educational and research perspective, it is the first point of reference for addressing the problem, in addition to providing updates at the center for specialists and residents in training.

Novelty of the Research

At the hospital, we do not have an evaluation of the results of treatment with total androgen deprivation in advanced prostate cancer patients. This work will allow us to obtain preliminary results related to the survival of these patients according to the risk classification at diagnosis, and the time of onset of signs of progression after treatment has been established.

Contributions

By evaluating the effectiveness of treatment with maximum androgen blockade in advanced

prostate cancer patients, we will contribute valid information to ongoing research that aims to evaluate the quality of adherence to the existing protocol at the center.

Chapter 02 / Capítulo 02

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Risk stratification and clinical basis

The history of cancer, in terms of its presence within communities, is relatively modern, as it is a genetic disease associated with triggering factors and the aging of the population. The first historical description dates to the Smith Papyrus. Subsequently, isolated descriptions of tumors have been repeated throughout history, and most of them have been treated individually and often anecdotally, as was the case with medicine in each era. Hippocrates coined the term "malignant ulcer" to describe cancer, or karkinos, which derives from the word crab, probably because the hard shell is like the consistency of malignant tumors.[13]

In Scotland, John Hunter suggested that cancer could be "removed" from the body, and in New York, Dr. William Halsted proposed that it could be cured through surgery. The latter proposed the hypothesis of the sequential spread of some cancers: first locally, then to regional lymph nodes, and later to distant sites. In this way, when the tumor is locally or locoregionally advanced, it is still curable. Halsted performed radical and bloc breast surgeries to remove the tumor and adjacent muscles plus axillary lymph nodes, achieving unprecedented cures and thus laying the foundations for modern cancer surgery, which continues to this day. Halsted's revolutionary, scientifically sound, and dogmatic concept quickly spread throughout the surgical medical community and began to be applied in other areas, such as head and neck, gynecological, and digestive cancers. In all these cases, the patient achieved his goal of curing cancer in the earliest stages of the disease.[14]

On the other hand, owing to Rudolf Virchow, in 1858, the origin of cancer was understood as a phenomenon that occurred within the cells themselves. The book Die Cellulare Pathologie indicates that the origin of diseases is at the cellular level.[15]

Dr. Farber laid the foundation for modern chemotherapy and became the father of medical oncology. He defined cancer as a disease that requires continuous research, which he actively encouraged and was sponsored in this regard by the American Cancer Society.[16]

Owing to Farber's contribution, not only are the foundations of chemotherapy treatment established, but radiotherapy also evolves significantly to establish modern treatments that are increasingly safe and effective. Hormone therapy in tumors with hormone receptors appears to be linked to the management of breast, prostate, and other cancers.

Prostate carcinoma is a malignant tumor that derives from the acinar and ductal epithelium of the prostate and can vary considerably in its glandular differentiation, anaplasia, behavior, metastatic patterns, and response to therapy. It is considered a "silent disease" because while cells transform and increase, up to 10 years can pass without symptoms appearing. The true cause of prostate carcinoma is unknown, but its growth is clearly influenced by sex hormones.[18,19,20]

Anatomical and histological overview

The prostate is a gray, tubuloalveolar exocrine gland with endocrine, testicular, and hypothalamic interrelationships and a high degree of oncogenic potential. This unpaired organ develops around the initial portion of the urethra, toward the pelvic cavity, immediately below the bladder, behind the pubis and anterior to the rectal ampulla. It is conical in shape, with its base attached to the bladder neck and its apex resting on the urogenital diaphragm. In adults, it measures 28 mm long, 40 mm wide, and 25 mm thick, weighing 20–25 g. It is rudimentary in

children, grows rapidly during puberty, and hypertrophies in elderly individuals.[21]

Anterior surface

This surface is located behind the lower portion of the pubic symphysis, from which it is separated by the Santorini venous plexus. The pubic–prostatic ligaments and the retropubic adipose panniculus extend between the prostate and the pubis.

Lateral surfaces

Bordered by the inner edges of the levator ani muscles and the vesical plexuses.

Posterior surface

In contact with the anterior surface of the rectum, the posterior surface is separated by only a small amount of loose connective tissue (Denonvilliers' fascia).

The base is related to the bladder and is concave. The anterior portion of the base has strong connections with the bladder; its dorsal portion has a deep transverse groove in the middle, at the level at which the ejaculatory ducts penetrate, also showing a grooved depression in which the seminal vesicles rest. [22]

Several anatomical models have been described for the study of the prostate. Randall described the existence of eight morphological types of prostatic adenoma. He considers the first five to be the most common. These are as follows: I. Adenoma composed of two lateral lobes. II. Middle commissural lobe. III. Middle commissural lobe and two lateral lobes. IV. Subcervical middle lobe. V. Subcervical lobe and two lateral lobes. VI. Middle commissural lobe, small subcervical lobe, and two lateral lobes. VII. Anterior lobe. VIII. Subtrigonal lobe. [23]

According to Gil-Vernet, the prostate cannot be considered a homogeneous structure; there is a cranial segment, a caudal segment, and an intermediate transitional portion.[24]

Babinski, M.A., described the zonal anatomy model of the prostate developed by McNeal, which is currently the most widely accepted model and considers the urethra, ejaculatory ducts, and sphincter complexes as reference points for describing the anatomical structure of the prostate.[25]

Transitional zone (TZ)

The transitional zone, prior to the development of BPH, constitutes approximately 5 % of the prostatic glandular tissue. It is located on both sides of the proximal urethra, and its glandular ducts drain into the proximal urethra at the level of *the veru montanum*. Prostatic calculi deposited within the ducts adjacent to *the veru* produce a hyperechoic Eiffel Tower pattern and define the caudal boundary of the transitional and central zones.[25]

The TZ is separated from the central and peripheral zones by the surgical capsule. In terms of its clinical implications, the TZ is the site of origin of BPH, lateral lobes, and 10–20 % of prostate tumors.

Central zone (CZ)

The central zone is a pyramid-shaped structure at the base of the prostate that constitutes 25 % of the prostatic tissue and narrows to the *veru montanum*. There is no central zone or transitional zone distal to the *veru*. [25]

The ejaculatory ducts, formed by the union of the ampulla deferens and the seminal vesicles, penetrate the central zone at the rear and run to both sides of *the veru*. This space is an area of anatomical weakness, as it lacks a capsule; it is called the invaginated extraprostatic space.

In terms of its clinical implications, the central zone is relatively resistant to tumors, accounting for 5–10 % of cancers. Once tumors, owing to their origin or spread, have reached this area, they tend to escape and cause infiltration and dilation of the ipsilateral seminal vesicle. The tumor subsequently obliterates the prostatic-seminal and vesico-seminal angles, infiltrating the seminal vesicles.[25]

Peripheral Zone (PZ)

The PZ constitutes 70 % of the prostate glandular tissue. It comprises the posterior, lateral, and apical aspects of the gland. Its ducts drain distally to the veru. The apex is an area of anatomical weakness due to the lack of a capsule, through which the tumor often escapes from the prostate, affecting the trapezoidal area bounded by the rectum, the apex, and the urethra.

In terms of its clinical implications, the PZ is the site of 70 % of tumors, which are usually located near the prostatic capsule. [25]

Arterial Irrigation

The main blood supply to the gland comes from the inferior vesical artery, the anterior branch of the hypogastric artery. The inferior vesical artery branches to the terminal ureter and seminal vesicle; it then penetrates the prostate at the prostatic–vesical junction, where the main trunk divides into two branches. One central branch supplies the urethra and periurethral glands, and the other peripheral branch supplies most of the prostate.

- *Venous drainage*: Although they usually accompany the arteries, the prostatic veins are very numerous. They join on the lateral and anterior sides, converging to form the venous plexus of Santorini with the deep dorsal vein of the penis, which drains into the hypogastric vein. There is an important connection between this plexus and the prevertebral venous plexus.
- *Lymphatic drainage*: The main type of lymphatic drainage is directed toward the internal, external, and obturator iliac lymph node groups. From here, it travels to the primitive iliac nodes and, from there, to the preaortic nodes.

Innervation of the prostate

The prostate receives abundant innervation from both divisions of the autonomic nervous system, which regulates the involuntary functions of the prostate. Sympathetic innervation comes from the hypogastric nerve, and parasympathetic innervation comes from the pelvic nerve.

The functional response of the prostate to the autonomic nervous system includes effects on the excretory epithelium, cholinergic innervation, and smooth muscle, adrenergic innervation, which is mediated mainly by alpha-1 receptors.

- *Veru Montanum*: This is an oval prominence located on the posterior wall with a vertical axis of 12 to 14 millimeters. The ejaculatory ducts open on either side of the *veru montanum*, and between them is the opening of the prostatic utricle.
- Prostatic utricle: This is a cavity-like formation between 4 and 12 millimeters in length, which begins at the level of the *veru montanum* and extends upward. Embryologically, it corresponds to the fused distal portion of the Müllerian duct.

- Ejaculatory ducts: These ducts are formed by the confluence of seminal vesicles with the ampullae of the vas deferens and represent the terminal portion of the spermatic tract. They are between 15 and 20 mm long and open on both sides of the *veru montanum*. [26]

Their main function is to produce prostatic fluid, which, once combined with other genital, testicular, seminal vesicle, Cowper's gland, and Littre's gland secretions, forms semen, which has an acidic pH but is neutralized by the other secretions that combine with it. Prostatic secretion is rich in proteins, inorganic salts, citrates, and enzymes such as fibrinolysins and proteolytics and is essential, although not indispensable, for male fertility, constituting the main support for sperm motility and vitality. [27]

The prostate is made up of different cell types, but most neoplasms develop on glandular cells and are called adenocarcinomas. This is the most common histological variety, accounting for 95 % of prostate cancers, and develops from the luminal cells of the prostate glands. It can occur in different forms, notably ductal adenocarcinoma, which originates in the prostate ducts and has a very poor prognosis because of its poor response to hormone treatment. Neuroendocrine cancer is a rare, chemoresistant subtype for which surgery is the only treatment option. Tumors that originate in the more peripheral prostate ducts can present as ordinary or acinar adenocarcinomas. There are other histological types of prostate cancer that account for 5 % of cases, such as sarcomas (rhabdomyosarcomas, leiomyosarcomas) and small cell, epidermoid, or squamous cell carcinomas. Primary prostatic urothelial carcinoma commonly affects the ducts and acini in patients with a history of carcinoma in situ (CIS) of the bladder who are treated for months or years with intravesical topical chemotherapy. Inflammatory prostatic myofibroblastic tumors can occur shortly after transurethral resection (TUR) or without a history of TUR. Fortunately, they occur much less frequently and are more aggressive.[28]

Risk factors for prostate cancer

Numerous genetic and environmental factors are considered causes of prostate cancer. Various genotypes associated with a risk of prostate cancer have been described. Somatic mutations that condition the transition to the malignant phenotype of the prostatic epithelium have also been reported. Slight reductions in phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase (PTEN) levels induce susceptibility to prostate cancer, and PTEN arrest is differential and progressive during prostate epithelial transition. Similarly, during the molecular and phenotypic progression of prostate cancer, growth factors lose their ability to regulate the biology of normal epithelial and stromal cells.[29]

Although the specific causes that determine the onset and progression of prostate cancer are still unknown, there is abundant evidence suggesting a predominant role of genetic and environmental factors in the evolution of this disease. Genetic predispositions with a high incidence in blood relatives of prostate cancer patients, with a 2- to 3-fold increased risk in men whose father or brother has prostate cancer, increasing to a relative risk of 5--11 if two or more close relatives are affected. Segregation analysis suggested that the most likely explanation for this familial clustering was autosomal dominant inheritance.[30]

It rarely occurs in people under 40 years of age, although there have been cases. Its incidence increases progressively in people over 65 years of age, reaching a peak in the 80 years of age group. It is more common in African Americans and Eastern Europeans, attributed to higher testosterone levels, and less common in Asians.[31]

Diet and nutritional supplements appear to be the most important secondary factors in assessing prostate cancer risk. A high-fat diet and excessive meat consumption have been associated with a modest increase in cancer risk in numerous studies, and recent reviews suggest that reducing these factors in the diet may lower cancer incidence. There is abundant evidence that the consumption of vegetables, especially cruciferous vegetables (cabbage, broccoli, kale) and tomatoes (lycopene), may be associated with a decrease in the incidence of prostate cancer. Fish consumption has also been shown to have a protective effect in two prospective studies, most likely because of the presence of a long-chain fatty acid in fish, namely, omega-3. These dietary habits may explain, at least in part, why the Japanese population (who consumes vegetables, fish, and minimal red meat) who emigrate to the West increases their incidence of prostate cancer when their dietary habits change.

No direct relationship has been observed between its onset and the ingestion of certain foods, but the chemopreventive action after ingesting foods rich in vitamin E, selenium, retinoids, fiber, and low in fat has been studied. Vitamin D (1,25-dihydroxyvitamin D) is an essential vitamin that is part of the steroid hormone superfamily. In humans, sources include both dietary intake and the conversion of an inactive form to an active form of vitamin D in the skin through exposure to sunlight. Interest in vitamin D as a determinant of prostate cancer risk stems from epidemiological studies showing that men living in northern latitudes with less exposure to ultraviolet rays from sunlight have a higher mortality rate from this disease. It also occurs frequently in older people, in whom vitamin D deficiency is more common owing to their lower exposure to sunlight and the age-related decline in the hydroxylases responsible for active synthesis.[34]

African Americans, whose skin melanin blocks ultraviolet radiation and inhibits its activation, have the highest incidence and mortality rates of prostate cancer worldwide. In addition, dietary intake of calcium-rich dairy products, which lower serum vitamin D levels, is associated with increased risk. Native Japanese individuals, whose diet is rich in fish, have a low incidence of adenocarcinoma. Similarly, prostate cancer cells express the vitamin D receptor, and several studies have demonstrated an antiproliferative effect on these cell lines because they induce cell cycle arrest.[34]

In 1993, a link between vasectomy and prostate cancer was proposed. Over time, the risk increases, so men who undergo vasectomy at a younger age have a greater risk. The biological mechanism by which vasectomy may predispose patients to cancer is unknown, although the presence of anti-sperm antibodies and the reduction in seminal androgen or androgen secretory activity have been proposed to explain this phenomenon.[35]

Cigarette smoking may be a risk factor for prostate cancer, as it is a source of cadmium exposure, increasing the concentration of circulating androgens and causing significant cellular oxidative stress. Case–control and cohort studies have produced conflicting results, and none have demonstrated a clear dose–response relationship.[36]

Chronic inflammation leading to excessive proliferation to replace damaged tissue contributes to the development of cancers associated with infection, possibly prostate cancer. Some epidemiological data suggest that a history of sexually transmitted infection or prostatitis is associated with an increased risk of prostate cancer. Histological evidence of inflammation, manifested by proliferative inflammatory atrophy, is common in prostate cancer and may represent a key biopathological process in its development. Genetic and histological observations

suggest that compromised cellular defenses against inflammatory oxidants are important in the initiation and promotion of prostate cancer.[37,38]

Genetic factors

Genetic and environmental factors are important in the origin and evolution of prostate cancer. Most cases are polygenic, but some hereditary forms may be determined by variants in one gene or relatively few genes. Several candidate susceptibility genes have been identified, including RNaseL (hereditary prostate cancer region 1 [HPCl]), 1q23-2S), ELAC2 (HPC2 region, 17p), and MSRl (8p22-23). Segregation studies also suggest the existence of susceptibility sites or loci on chromosome lq42.2 43 (PCAP).

Among the known susceptibility genes, HPCl is the best characterized, and its existence has been suggested by screening families with hereditary prostate cancer. It is an autosomal dominant gene with high penetrance and encodes the enzyme RNaseL, which has antiviral and proapoptotic activity. Commonly observed RNaseL variants result in reduced enzyme activity and are associated with an increased risk for this disease.[39]

A variety of missense RNaseL mutations have been identified in families with hereditary diseases. Among these mutations, the R462Q SNP, resulting from an arginine-to-glutamine substitution, has been shown to be associated with an increased risk. Cell lines with this allele variant were shown to have reduced RNaseL activity, leading to impaired apoptosis, which presumably favors the accumulation of genetic defects that result in the development of cancer.[40]

Insulin-like growth factor (IGF)-l is a peptide hormone that promotes growth in adolescence and childhood and is associated with lean body mass in adults. IGF-l promotes cell proliferation and inhibits apoptosis in normal cells and prostate tumor cells. IGF-l is bound to binding proteins, the most prominent of which is insulin-like growth factor-binding protein 3 (IGFBP-3). In the prostate, IGFBP-3 promotes apoptosis and may mediate growth inhibition by 1,25-dihydroxyvitamin D. IGFBP-3 can be fragmented by PSA, thereby reducing its proapoptotic activity.[41]

Leptin, a peptide hormone produced by adipocytes, contributes to body weight control by suppressing appetite and modulating energy use. Leptin has been shown to stimulate the proliferation of the androgen-independent prostate cancer cell lines DUl45 and PC-3. In addition, leptin induces the expression of vascular endothelial growth factor (VEGF) and basal fibroblast growth factor (BFGF) and stimulates cell migration. Energy imbalance, perhaps mediated by leptin, has emerged as a possible contributor to prostate cancer progression, leading to metastasis and death.[42]

Alterations in AR signaling can occur at various levels, all of which can potentially contribute to the development or progression of prostate cancer. These alterations include changes in the ligand concentration in tumor cells, increased expression of androgen receptor proteins, mutations leading to structural and functional alterations, changes in coregulatory molecules, and factors leading to ligand-independent receptor activation. A recent study showed that gene inactivation of androgen receptors causes regression of prostate cancer, including castration-resistant prostate cancer, suggesting that androgen receptors are of biological and clinical importance even after androgen deprivation.[43,44]

NKX3-1 is an androgen-regulated, prostate-specific gene located on chromosome 8p21 and belongs to the homeobox gene family. Mice deficient in NKX3-1 exhibit defects in the morphogenesis of the prostatic ducts and in the production of secretory proteins and suffer from dysplasia, PIN, and cancer as they age. The loss of one or both NKX3-1 alleles becomes more common in prostate lesions as they progress from PIN to local, metastatic, and androgen-independent tumors.[45]

PTEN, located on chromosome lOq23, is one of the most well-studied tumor suppressor genes in prostate cancer. Genetic, functional, and molecular studies suggest that PTEN plays a role in the initiation and progression of this disease. PTEN deletion has been shown to induce prostate cancer in mice. Loss of PTEN function is observed in the PIN and is associated with a high Gleason score and advanced stage.[46]

Among classic oncogenes, alterations in the tumor suppressor genes RBl and TP53 are common in patients with metastatic disease and in the absence of hormone sensitivity, suggesting that these genes play a role in tumor progression. Alterations in c-MYC, c-ERBB2, and BCL-2 have also been observed in advanced and hormone-resistant prostate cancer but are uncommon in low-grade or low-stage disease, suggesting that proto-oncogene mutations usually occur as secondary events associated with tumor progression.[47]

TP27 belongs to the CIP/KIP family of cyclin-dependent kinase (CDK) inhibitors and regulates cell cycle progression from the G1 phase to the S phase. The loss of TP27 can accelerate tumorigenesis by allowing cells to progress unregulated through the cell cycle.

Vascular endothelial growth factor (VEGF), which is an important mediator of tumor angiogenesis, is expressed in most prostate cancers; increased expression of this substance has been associated with disease progression and survival. VEGF is regulated by androgens, suggesting a possible pathway by which androgen regulates prostate cancer growth.[48]

AMACR (racemase) is an enzyme that plays a critical role in the metabolism of branched-chain fatty acids. Compared with that in localized disease, AMACR expression has been shown to be lower in metastatic prostate cancer, and this enzyme has been associated with cancer-specific survival.

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein expressed by the epithelium of prostate cancer and in the neovasculature of other solid tumors. PSMA overexpression is observed after androgen deprivation and in hormone-resistant disease and is the basis for imaging studies using anti-PSMA monoclonal antibodies.[49]

PCA3 is a urinary biomarker that has been extensively researched. Urinary concentrations do not appear to be elevated with increasing prostate size, but they are associated with tumor volume. To increase the sensitivity of this test, urine samples are collected after a “thorough” digital rectal exam, which, in conceptual terms, loosens and sloughs off cells within the prostate and thus increases the likelihood of detection.[50]

The E-cadherin gene, located on chromosome 16q22.1, encodes a transmembrane glycoprotein that mediates intercellular adhesion. Its expression is reduced in a significant percentage of prostate cancers, particularly poorly differentiated tumors, and cadherin E expression in prostate cancer is inversely associated with grade, stage, metastasis, recurrence, and survival.[51]

Clinical picture

Prostate cancer presents a wide spectrum of clinical behaviors, being indolent in some individuals and aggressive and rapidly metastatic in others. The rate of progression is therefore highly variable. Life expectancy decreases as the disease progresses to a more advanced stage. There is no specific clinical picture for prostate cancer. In the early stages, when the tumor is confined to the prostate, it may be asymptomatic or accompanied by mild obstructive symptoms attributable to benign hyperplasia or local infiltration, with infections secondary to obstruction and the appearance of distant metastases.[52]

The possibility of concomitant prostatic hyperplasia is described, with obstructive symptoms being due more to this condition than to the cancer itself, referring to urination disorders caused by nocturnal pollakiuria, delayed urination, decreased urinary stream force, and urinary retention. They also refer to burning during urination and urgent urination, which can lead to paradoxical incontinence. The study of benign prostatic hyperplasia may lead to a diagnosis of prostate adenocarcinoma.[53]

Hematuria occurs when the urethral mucosa, bladder neck, and trigone infiltrate, accompanied by severe unilateral or bilateral lumbar pain caused by ureterohydronephrosis. Hemospermia and erectile dysfunction have been described. In advanced stages, asthenia, anorexia, and weight loss occur as manifestations of obstructive renal failure.

In disseminated disease, bone metastases occur, most commonly in the pelvis and lumbar spine. Patients may report radicular pain, functional impotence, pathological fractures, and spinal cord compression. Lymphedema of the lower limbs is caused by compression of regional lymph node bundles at the level of the pelvis and bifurcation of the common iliac artery, and anemia is secondary to kidney damage or an expression of the disease itself.[54]

Physical examination

A digital rectal exam is the most important physical examination for suspecting the presence of prostate cancer, with increased consistency sometimes being a warning sign. When the tumor is localized, an indurated area or nodule can be felt in a gland enlarged by hyperplasia or induration of one or both lobes. In a more advanced stage, a prostate with a stony or woody consistency, irregular surface, imprecise boundaries, fixed and painless is detected.

When complete urinary retention occurs, examination of the abdomen reveals a central tumor in the hypogastrium, which is dull to the touch and painful, reaching the umbilical region, which is consistent with a bladder balloon.

The inguinal regions were examined to detect possible adenomegaly, and the lower limbs were examined for the presence or absence of lymphedema, which may be asymmetrical and result from compression of the venous vessels by metastatic adenomegaly or compromised lymphatic return.[55]

Complementary tests

The determination of prostate-specific antigen (PSA) has revolutionized the diagnosis and monitoring of prostate cancer over the last two decades. It is a glycoprotein of the kallikrein family produced almost exclusively by prostate epithelial cells. It is found mainly in semen, although it is also present in small amounts in the blood. It is measured in nanograms per milliliter (ng/mL). The likelihood of cancer increases as PSA levels rise, but there is no established

threshold value that can indicate with certainty whether a man has prostate cancer. Elevations above 4 ng/mL raise suspicion of malignant pathologies, although lower levels, such as 2,5 or 3 ng/mL, are also recommended.[56]

During carcinogenesis, its level often increases to more than 4 ng/mL. However, a concentration less than 4 ng/mL does not guarantee that a patient does not have cancer. Approximately 15 % of patients with a PSA level less than 4 are diagnosed with prostate cancer if a biopsy is performed. PSA levels between 4 and 10 are often referred to as the "borderline range," with a 1 in 4 chance of prostate cancer. If the PSA is above 10, the risk is greater than 50 %. For practical purposes, it is an organ-specific marker, not a cancer-specific marker.[57]

Conditions such as benign prostatic hyperplasia, a noncancerous enlargement of the prostate that affects many men as they age, can increase PSA levels. With age, levels normally rise slowly, even if one has no prostate abnormalities. Infection or inflammation of the prostate gland has been described. Ejaculation can cause a brief increase in PSA levels. Cycling has been shown in studies to increase PSA levels (possibly because the seat puts pressure on the prostate), although not everyone agrees with this. Certain urological procedures, such as prostate biopsy, permanent catheterization, or cystoscopy, have also been described. A rectal exam slightly increases it, although not all research has confirmed this. Despite this, if a PSA test and a rectal exam are performed during the consultation, some doctors recommend drawing blood for the test before performing the rectal exam. Certain medications, such as male hormones (testosterone) or others, that increase testosterone levels can cause an increase.[58]

There are special types of PSA tests, with the total PSA level being obtained during routine screening. When the result is inconclusive, different types of tests may be considered to help decide whether a prostate biopsy is necessary. PSA is found in the blood in two main forms: one is attached to blood proteins, while the other is free or unattached. The free PSA percentage (%fPSA) is the ratio of the amount of PSA circulating freely to the total PSA level. The percentage of free PSA is lower in men with prostate cancer than in men without the disease, and a biopsy is recommended if the percentage is between 10 % and 25 %. Using these cutoff values allows most cancers to be detected and helps avoid unnecessary biopsies. This test is widely used, but not all doctors agree that 25 % is the best cutoff value for deciding whether a biopsy is necessary. In addition, the cutoff value may change depending on the overall PSA level.[59,60]

Complex PSA directly measures the amount of PSA that is attached to other proteins (the portion of PSA that is not "free"). This test can be performed instead of checking total and free PSAs and provides the same amount of information, but it is not widely used.

The PSA velocity is not a separate test but a measure of how quickly the PSA velocity increases over time. Normally, levels increase slowly with age. Some studies have shown that PSA levels increase more rapidly in men with cancer, although studies have not shown that velocity is more useful than the PSA level alone in detecting prostate cancer.

PSA density (PSAD) is used in men with large prostate glands to try to correct for variations due to prostate size. The volume of the prostate is measured via transrectal ultrasound, and the PSA level is divided by the prostate volume. A high density indicates a high probability of cancer. Density has not been shown to be as useful as the free PSA percentage test.[61]

Age-adjusted PSA values.[62]

Table 2.1. Age-adjusted PSA values

Age (years)	Normal PSA range (ng/mL)
41	0-2,5
51	0-3,5
61-70	0-4,5
71-80	0-6,5

There are tests that combine different types of PSAs to obtain an overall score that reflects the likelihood of a man having prostate cancer. These tests include the Prostate Health Index (PHI), which combines the results of total PSA, free PSA, and proPSA. The 4K score test combines the results of total PSA, free PSA, intact PSA, and human kallikrein 2 (hK2), along with other factors. These tests can be useful with a slightly elevated PSA to help determine whether to undergo a prostate biopsy or to determine whether a man who has a negative prostate biopsy should undergo another biopsy.

Transrectal ultrasound technology has become the mainstay of numerous image-guided prostate procedures, such as prostate biopsy, brachytherapy, cryotherapy, and high-intensity focused ultrasound. The classic zonal anatomy of the prostate is not evident on transrectal ultrasound, but the peripheral zone can usually be distinguished from the transition zone, allowing biopsies to be reliably targeted to the peripheral zone, which is where cancers are most often found. There are several formulas for determining prostate volume on transrectal ultrasound. Hypoechoic foci observed on grayscale transrectal ultrasound should be considered suggestive of adenocarcinoma and should be included in the biopsy specimen. However, up to 39 % of cancers are not visible via transrectal ultrasound.[64]

Currently, systematic PSA screening in asymptomatic men has led to the adoption of transrectal ultrasound-guided biopsy as the gold standard for routine histopathological examination of the prostate. The presence of focal nodules on digital rectal examination will, in any case, prompt a biopsy via the transrectal ultrasound technique, regardless of PSA concentration. Transrectal ultrasound-guided fine needle aspiration biopsy remains the gold standard procedure for the diagnosis of prostate cancer.[65]

Prostate biopsy may also be indicated on the basis of the pathological analysis of previous biopsy samples. In men who have undergone a prostate biopsy and are found to have only high-grade prostatic intraepithelial neoplasia or small atypical acinar proliferation, a follow-up biopsy should be performed in three to six months. The risks and benefits of the procedure should be explained, and informed consent should be obtained. All anticoagulant and nonsteroidal anti-inflammatory drug (NSAID) therapy should be discontinued 7 to 10 days prior to prostate biopsy. In patients with underlying coagulopathy or who are receiving warfarin, a prostate biopsy should not be performed until the international normalized ratio has been corrected to below 1,5.[66]

A wide variety of prophylactic regimens using oral and intravenous antibiotics have been studied, with widely varying opinions on their use. Patients are instructed to administer a cleansing enema at home before surgery. The use of enemas reduces the amount of stool in the rectum, thus providing a better acoustic window for visualization of the prostate. The effect of enemas on reducing infections is debated, although it seems logical that a cleansing enema and

an empty rectal vault could reduce bacterial colonization of the prostate.[67]

Various systematic biopsy schemes have been described, including the sextant biopsy scheme originally proposed by Hodge, Presti's 10-core biopsy, the 12-core or double sextant biopsy, and Eskew's 5-region 13-core biopsy. The most common complications described are postbiopsy infection, which can range from urinary tract infection to acute prostatitis, presenting with bacteremia, and cases of septic shock, hemorrhage (rectal bleeding, hemospermia, hematuria, or urethral bleeding), and vasovagal response have been described. In addition, in patients who cannot be accessed rectally, the transurethral route can be used, although its use is controversial, and the perineal route can be used in patients without a rectum.[68]

Diagnosis

The diagnosis of the disease is histological, whether the sample is the result of an ultrasound-guided or finger-guided transrectal biopsy or a biopsy of the sample obtained by adenomectomy or TUR.

We consider that age, personal and family medical history, clinical presentation, digital rectal examination, PSA level, and transrectal ultrasound provide sufficient information to indicate the need for a biopsy.

The results of the biopsy provide information on the degree of cellular differentiation of the tumor, the Gleason score, and the group to which it belongs. However, this information is insufficient to determine the stage of the disease at diagnosis, which is why the results are supplemented with laboratory tests such as a complete blood count, blood chemistry, PSA, alkaline phosphatase, and urine culture. In addition to chest X-ray, abdominal, bladder, and prostate ultrasonography; bone scans; and tomographic studies and SPECT/CT, if the above methods are inconclusive for patient staging.

Anatomopathological diagnosis

The anatomopathological diagnosis is made after a prostate biopsy and is based on the recognition of precise microscopic criteria such as anarchic and infiltrating glandular proliferation, loss of the basal layer of the tumor glands, irregular nuclei that are enlarged and hyperchromatic, prominent nucleoli, and perineural infiltration. Cancer is usually multicentric and develops from intraductal precancerous lesions (PINs).[69] In difficult cases, combined immunohistochemical studies aid in diagnosis.

The histological grading of prostate carcinoma was proposed by Donald Gleason in the 1960s and 1970s.[9,10] This grading system has been revised and modified in some respects since its initial conception, following the consensus conferences of the International Society of Urological Pathology (ISUP). These changes are justified to adapt to the current circumstances of prostate carcinoma diagnosis, which differ in part from those in which Gleason established a grading system.

The great success of the Gleason grading system, which has been in use for more than five decades, is that it considers and assesses the tumor heterogeneity of prostate carcinoma and does not assign the most severe grade. The grading is based on two concepts: the degree of glandular differentiation and the relationship between the glands and the surrounding stroma. Gleason established five patterns that reflected a continuum of differentiation, with 1 being the best differentiated pattern, with well-differentiated, round, regularly spaced glands with little

stroma between them and relatively uniform glands, forming part of a well-defined nodule. At the other extreme, the worst differentiated pattern is pattern 5, i.e., those carcinomas that no longer have any glandular differentiation, which grow in solid nests, with loose cells in rows. Patterns 2--4 would be intermediate grades, such that the differentiation of independent glands is maintained in patterns 2 and 3, with the difference that in Grade 2, the glands also form part of a nodule, although with greater variability in size, shape, and separation between them than in Pattern 1. Therefore, to establish the presence of patterns 1 and 2, a fundamental criterion is that the tumor glands form part of a defined nodule. Since this criterion cannot be applied to the cylinders obtained from the 18G needles generally used, these patterns cannot be identified in this type of material. In addition, these low-grade adenocarcinomas are more common in the transition and anterior zones of the prostate, which are not usually included in needle biopsies. Therefore, in prostate biopsies, the lowest pattern recognized is 3, and the lowest Gleason score is 3 + 3 = 6. In pattern 3, the glands remain independent, well-formed, and luminal, although they are more angular, more irregular, and show infiltrative behavior in relation to the stroma, without delimitation in a nodule. This is the most frequently observed pattern, both when it is defined by the Gleason score and when it is currently defined. Pattern 4 is defined by the presence of glandular fusion; the glands are no longer independent and appear malformed or fused, even forming cribriform nests of varying sizes and shapes. Pattern 4 will only occur in a group of poorly formed glands when it is clearly ruled out that they do not correspond to artifacts or tangential sections of pattern 3 glands.

The score is the result of the sum of the two grades most prevalent in the tumor on a scale of up to 10.[30] In the case of multiple cylinders of different grades, assigning a separate Gleason grade to each cylinder that is sent in a separate container and/or with the designated location and an overall score in the case that the cylinders are sent in a single container or fragmented is recommended. It is optional to report an overall grade for the entire case. It is the most powerful independent prognostic factor for clinical behavior and response to treatment. Thus, the Gleason score is one of the parameters incorporated into nomograms that predict the risk of recurrence after treatment.

Over the years, Gleason grades have been grouped according to prognosis. The most frequently used classification systems are those of the National Comprehensive Cancer Network (NCCN) and the D'Amico classification system: GSSs 2--6, 7, 8, and 9--10. In the last decade, Gleason grades 2--5 have virtually disappeared. In summary, there are prognostic differences depending on whether pattern 4 is secondary or primary (3 + 4 vs. 4 + 3). Mortality in patients with a Gleason score of 4 + 3 = 7 is three times greater than that in patients with a Gleason score of 3 + 4 = 7. J.I. Epstein's group at Johns Hopkins Hospital proposed supplementing the prognostic information provided by the Gleason histological grade by grouping Gleason grades into five prognostic categories, known as grades 1--5. This proposal was based on an initial study with biopsies and radical prostatectomies, which demonstrated a strong correlation with biochemical recurrence.

The impact of these new grade groups on clinical practice is their correlation with the behavior of prostate cancer patients, as they correlate with prognosis and, consequently, guide urologists in therapeutic decision-making. Grade 1 disease is a homogeneous group with an excellent prognosis, with a 95 % cure rate at 5 years, without lymph node metastasis, even in patients with extraprostatic extension or positive margins. In general, these patients have a small tumor volume (0,5 to 2 cc). These patients may be candidates for active surveillance. However, it should not be forgotten that up to 20 % of patients have higher-grade tumors that have not been

included in biopsies. The grade 2 group has a good prognosis, with metastasis rarely occurring. The grade 3 group had a significantly worse prognosis. In group 2, the percentage of pattern 4 patients was important, given that active surveillance could also be considered in patients with small percentages (5–10 %). Patients in Grade 2 groups with a higher percentage of Patients in Pattern 4 than mentioned above and those in Grade 3 were candidates for definitive therapies, such as prostatectomy. Patients in Group 4 had a better prognosis than did those in Group 5, which included very aggressive tumors. Patients in groups 4 and 5 needed adjuvant therapy or radiotherapy. In the coming years, the grade 4 group will probably be redefined in terms of the prognostic differences in the presence of pattern 5, which would imply a worse prognosis than the mere presence of patterns 4 + 4 = 8.

The pathology report should explicitly state the location of the positive cylinders, which will give an idea of the involvement of one or both prostate lobes. This location can only be based on the information received in the packages. It is therefore very important that the cylinders are sent back such that their locations are clearly identified. Staging data related to extraprostatic extension are very difficult to assess in prostate biopsies. It is only definitive in cases where infiltration of the seminal vesicle wall is identified if it is included in the casts. The presence of tumor glands in skeletal muscle, adipose tissue, or ganglion cells does not guarantee extraprostatic extension. Although uncommon, lymphovascular invasion can be found. Perineural infiltration is associated with a greater incidence of extraprostatic extension in radical prostatectomy, as it is common in advanced disease, although its value as an independent factor is questioned. In clinically localized disease, these data may be of interest, particularly if large nerves are affected, when the possibility of active surveillance is considered. The presence of perineural invasion is not fully determined to be an independent factor for PSA recurrence in some surgical series.

Today, the tumor stage (TNM) of prostate cancer can be characterized optimally.

The disease is classified as:

- Tx if the primary tumor cannot be evaluated
- T0 if there is no evidence of a primary tumor
- T1 is considered when it is not clinically detectable by digital rectal examination or imaging.
    - T1a if detected incidentally in <5 % of the tissue in a histological sample of the prostate.
    - T1b if incidentally detected in >5 % of the tissue in a histological sample from the prostate. Tc is detected in a histological sample from the prostate because of elevated PSA values.
- T2 when the disease is confined within the prostate.
    - T2a if half or less of a lobe is affected.
    - T2b if more than half of one lobe but not both lobes are affected.
    - T2c if both lobes of the prostate are affected by the disease.
- T3 when the disease extends through the prostatic capsule.
    - T3a when the spread is unilateral or bilateral extracapsular.
    - T3b when the seminal vesicles are affected by the disease.
- T4 when the tumor attaches to or invades adjacent anatomical structures beyond the seminal vesicles (bladder, levator muscles, and/or pelvic wall).[36]
- Nx. Lymph node involvement cannot be assessed.
- N0. No lymph node involvement

- N1. Regional lymph node involvement
- Mx. Metastasis cannot be assessed
- M0. No distant metastasis
- M1. Distant metastasis
    - M1a. Distant lymph node involvement.
    - M1b. Bone involvement.
    - M1c. Other locations

Since 1998, prostate cancer has traditionally been categorized into different risk groups based on Anthony D'Amico's classification into three prognostic groups (low, intermediate, and high) based on studies of radical prostatectomy and radiotherapy and the analysis of biochemical recurrence and cancer-specific mortality. Since then, clinicians have used various risk classifications, almost all of which are based on three clinical parameters: prostate-specific antigen (PSA) level, Gleason score from biopsy, and local stage. When assessing the significant limitations of this type of categorization, it is important to remember that two of the three parameters (Gleason score and staging) vary considerably after analysis of the surgical specimen, as is well known. In fact, there is significant prognostic heterogeneity when traditional stratification schemes are used, with 5-year progression-free survival rates varying between 49 % and 80 %. The objective of these classifications is to stratify patients into groups with prognostic value that allow us to identify which patients will benefit from one therapeutic option or another and predict their evolution, that is, to know which patients will be cured with radical treatment and which will require multimodal treatment.

Low risk patient	Intermediate risk patient	High risk patient
T1c-T2a and/or PSA ≤ 10 ng/ml and/or Gleason ≤ 6	Tb2 or 10-20 ng/ml and/or Gleason 7	T2c and/or PSA > 20 ng/ml and/or Gleason > 7

Figure 2.1. D´AMICO Cancer risk classification

Low risk	Intermediate risk	High risk	
PSA < 10 ng/ml and GS < 7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/ml or GS 7 (ISUP grade 2/3) or cT2b.	PSA > 20 ng/ml or GS > 7 (ISUP grade 4/5) or cT2c.	Any PSA Any GS cT3-4 or cN+ Any ISUP grade
Localized			Locally advanced

Figure 2.2. EUA Guidelines on prostate cancer 1998

Figures 1,2 and 3 show the three classifications most frequently used by urologists in staging the risk of localized tumors: the classic D'Amico classification (figure 1), the European Urology Association (EAU) classification (figure 2), and the new version of the National Comprehensive Cancer Network (NCCN) classification (figure 3).

It is interesting to note how the new classifications currently consider, from a clinical and conceptual management point of view, localized and locally advanced tumors together under the same umbrella. In fact, tumors with extracapsular extension (T3) that are locally advanced are included in the high-risk category in both guidelines. T3b (vesicle invasion) and T4 (adjacent organ) tumors are labeled as very high risk by the NCCN guidelines. These American guidelines, however, do not consider cT2c tumors to be high risk but rather intermediate risk. The Radiation

Therapy Oncology Group (RTOG) high-risk classification includes two types of tumors: those with a Gleason score ≥ 8 and those with a Gleason score of 7 plus ≥ cT3a or N1, minimizing the value of the PSA level.

Risk group	
Very low	- T1c and - Gleason ≤ 6/GG 1 and - PSA < 10 ng/ml and - Fewer than 3 positive cores with ≤ 50% cancer in each and - PSA density < 0.15 ng/ml/g
Low	- T1-T2a and - Gleason ≤ 6/GG 1 and - PSA < 10 ng/ml
Favorable intermediate	- T2b-T2c or - Gleason score 3 + 4/GG 2 or - PSA 10-20 ng/ml and - Positive biopsy percentage < 50%
Unfavorable intermediate	- T2b-T2c or - Gleason score 3 + 4/GG 2 or Gleason score 4 + 3/GG 3 or - PSA 10-20 ng/ml
High	- T3a or - Gleason 8/GG 4 or - Gleason 4 + 5 /GG 5 or - PSA < 20 ng/ml
Very high	- T3b-T4 or - Primary Gleason 5 or - > 4 cores with Gleason 8-10/GG 4 or 5

Figure 2.3. NCCN Risk classification 2018. V2

A recent consensus published in 2017 by three Spanish societies involved in the management of the disease, Urology (AEU), Radiation Oncology (SEOR), and Medical Oncology (SEOM), determined that the definition of high risk includes all patients diagnosed with PSA > 20 ng/ml and/or Gleason > 7 and/or cT3a-cT4, thus including not only high localized risk but also high locally advanced risk and very high risk (T3b-T4).

Table 2.2. Consensus definition of high risk by the three societies	
PSA	> 20 ng/ml or,
Gleason level	> 7 or,
Clinical state	T3a-T4

In 2017, the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) standard staging system incorporated pretreatment PSA data and the new 2014 histological classification of the International Society for Urological Pathology (ISUP) into its traditional TNM system to divide patients into prognostic categories. Recent classifications include such a basic parameter as the measurement of tumor involvement in biopsy samples based on evidence that the percentage of involvement is significantly associated with cancer mortality. It is obvious that a cT3a patient with PSA = 12 ng/ml and a Gleason score of 4 + 4 in 2/12 cylinders cannot have the same potential for aggressiveness as another patient with cT3b, a PSA = 19 ng/ml, and a Gleason score of 4 + 5 in 10/12 affected biopsies, even though both are labeled high-risk cancers.

The percentage of affected cylinders should be considered by most authors as the fourth basic factor in the correct categorization of these patients, with a value significantly greater than that of the PSA.

When T is...	And N is...	And M is...	And PSA is...	And Grade is...	Then, the Stage is...
cT1a-c, cT2a	N0	M0	< 10	1	I
pT2	N0	M0	< 10	1	I
cT1a-c, cT2a, pT2	N0	M0	≥ 10 < 20	1	IIA
cT2b-c	N0	M0	< 20	1	IIA
T1-2	N0	M0	< 20	2	IIB
T1-2	N0	M0	< 20	3	IIC
T1-2	N0	M0	< 20	4	IIC
T1-2	N0	M0	≥ 20	1-4	IIIA
T3-4	N0	M0	Any value	1-4	IIIB
Any T	N0	M0	Any value	5	IIIC
Any T	N1	M0	Any value	Any Grade	IVA
Any T	Any N	M0	Any value	Any Grade	IVB

Figure 2.4. TNM stages and prognostic classification of prostate cancer, AJCC UICC 2017

The Cancer of the Prostate Risk Assessment (CAPRA) score was developed to improve risk classification and includes age and the percentage of biopsies affected by cancer (>33 %) as two parameters to be added to the three classic parameters in predicting cancer-specific mortality. Patients with a score of 6 or higher are considered high risk. The evaluation of the number of affected cylinders is also included in the NCCN V2 2017 very high-risk classification, which considers patients with >4 positive biopsies with a Gleason score of 8–10 (GG 4/5) to be at very high risk. Similarly, patients with four or more positive cylinders with a Gleason score ≥ 8 are considered very high risk by the RTOG.

Prostate cells are physiologically dependent on androgens to stimulate their growth, function, and proliferation. Testosterone, although not oncogenic, is essential for the growth and perpetuation of tumor cells. The testes are the source of most androgens, with only 5–10 % (androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate) derived from adrenal biosynthesis.[43]

Testosterone secretion is regulated by the hypothalamic–pituitary–gonadal axis. Hypothalamic gonadotropin-releasing hormone (GnRH) stimulates the adenohypophysis to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates the Leydig cells of the testes to secrete testosterone. Inside prostate cells, the enzyme 5-alpha-reductase converts testosterone into 5-alpha-dihydrotestosterone (DHT). Circulating testosterone is aromatized and converted peripherally into estrogens, which, together with circulating androgens, exert

negative feedback control over hypothalamic LH secretion.[44]

Variable	Corresponding Points
PSA at diagnosis, ng/ml	
<6.0	0
6.0-10	1
10.01-20	2
20.1-30	3
>30	4
Gleason grade on biopsy, primary/secondary pattern	
1-3/1-3	0
1-3/4-5	1
4-5/1-5	3
Age at diagnosis (years)	
< 50	0
> 50	1
Clinical tumor stage	
T1a-T2c	0
T3a	1
% of biopsy cores positive for cancer	
≤ 33	0
> 33	1

Figure 2.5. CAPRA risk classification (Cancer of the prostate risk assessment)

When prostate cells are deprived of androgen stimulation, they undergo apoptosis, and any treatment that ultimately causes suppression of androgen activity is called androgen deprivation therapy (ADT).[45]

Chapter 03 / Capítulo 03

Advanced Prostate Adenocarcinoma and Androgen Deprivation Therapy. Clinical Outcomes, Risk Stratification, and Therapeutic Results
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Androgen deprivation therapy and treatment rationale

A brief history of androgen deprivation

In 1941, Huggins and Hodges published "Studies on prostate cancer. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate." This work demonstrated for the first time that reducing testosterone levels through surgical castration (orchiectomy) or estrogen injection induced significant regression of prostate cancer, as verified by biochemical markers such as acid phosphatase and alkaline phosphatase, as well as rapid relief of symptoms when the cancer was metastatic and symptomatic. This work paves the way for what is known as androgen deprivation therapy (ADT), which is now considered a key element in the therapeutic arsenal for the treatment of prostate cancer.

Methods of androgen deprivation

There are methods of androgen deprivation that can be achieved by suppressing the production of testicular androgens or by inhibiting their action. The former can be achieved through surgical castration (orchiectomy) or, preferably, through medical castration (hormone treatment). This treatment can normalize PSA in more than 90 % of patients and significantly reduce tumor size in 80–90 % of them. The latter would be achieved by competitive inhibition at the receptor level in prostate cells with so-called "antiandrogens." In turn, both methods can be combined, achieving what is called a "complete androgen blockade," also referred to as "maximum or total" (CAB).

Different pharmacological groups have advantages and disadvantages in terms of their effects, efficacy, adverse drug reactions, and short- and long-term effects. Therefore, prostate cancer treatment should be individualized according to the needs of the patient.

Bilateral Orchiectomy

Bilateral orchiectomy, whether total or a subcapsular technique, i.e., with preservation of the tunica albuginea and epididymis, is a simple surgical procedure with virtually no complications that is easy to perform under local anesthesia. It is the fastest way to achieve castration levels, usually in less than 12 hours.[49]

As it is a relatively simple technique, its irreversibility and rejection because it is considered an "attack on virility," together with the possibility of achieving castration with equally effective pharmacological options, have led to a gradual decline in the use of bilateral orchiectomy. It is the gold standard method of androgen deprivation, the goal of which is to achieve the so-called "castration concentration" or testosterone concentration that is reached through surgical castration. This concentration has been established at < 50 ng/dl, although some authors propose a lower value (< 20 ng/dl) following the development of more accurate methods of testosterone assessment.

Medical Castration

In medical castration, the first hormonal treatment used was estrogen, whose use is associated with serious thrombogenic adverse effects. Years later, in the 1980s, the discovery of the GnRH receptor and the synthesis of its first analog (LH-releasing hormone agonist [LHRH]) definitively established androgen blockade. However, there is currently renewed interest in estrogens, mainly due to the adverse effects and high cost associated with the long-term use of LHRH agonists, as well as new scientific evidence in favor of estrogens.

LHRH agonists, which have been used for more than 20 years in the treatment of advanced prostate cancer, are the main tools used today. They achieve permanent desensitization of pituitary LHRH receptors through permanent occupation, which suppresses the release of LH and FSH and, therefore, the production of testosterone. The "castration concentration" is achieved within 2–4 weeks in up to 90 % of patients. Currently available LHRH agonists include the active ingredients buserelin, goserelin, leuprorelin, triptorelin, and histrelin.

They are usually administered as delayed-release injections on a regimen of every 1, 2, 3, 6, or 12 months. After the first injection (2–3 days), a "testosterone surge" or "flare-up" effect usually occurs, which typically persists during the first week of treatment. The different active ingredients have similar effectiveness, although there are practical differences that must be considered in daily clinical practice, including their form of administration and availability for immediate use.

LHRH antagonists, which act on the same receptors as LHRH agonists, have recently been developed. However, unlike agonists, they bind immediately to receptors, resulting in immediate inhibition of the release of LH, FSH, and testosterone. This avoids the "flare effect" associated with the use of LHRH agonists. Despite the appeal of their mode of action, studies supporting their use are limited. In a recent meta-analysis, LHRH antagonists were shown to have similar efficacy to leuprorelin and goserelin. The absence of a "flare effect" has also been demonstrated.

Inhibition of androgen action

Antiandrogens compete with testosterone and dihydrotestosterone at the receptor level in the prostate cell nucleus, promoting apoptosis and inhibiting prostate cancer growth. They play an important role when starting therapy with LHRH agonists because they prevent the "flare effect." This prevention is especially important in symptomatic patients or when this effect can cause serious complications. These compounds are classified as steroidal or nonsteroidal antiandrogens based on their chemical structure. The former are drugs from the progestin group with dual effects: at the peripheral level, they compete with androgens at the receptor level, whereas at the central level, they have a progestational effect, preventing the release of gonadotropins via negative feedback, which results in a reduction in plasma testosterone levels. Drugs of this type include cyproterone acetate, megestrol acetate, and medroxyprogesterone acetate. Since steroidal antiandrogens decrease testosterone concentrations, the main pharmacological side effects are loss of libido and erectile dysfunction, whereas gynecomastia is very rare. Nonpharmacological side effects include cardiovascular toxicity and hepatotoxicity.[61]

The latter only compete with androgens at the receptor level, so they do not decrease the testosterone concentration, which remains normal and may even rise slightly. Drugs of this type include nilutamide, flutamide, and bicalutamide.

Compared with castration, the use of nonsteroidal antiandrogens as monotherapies has been promoted based on improved quality of life and treatment compliance. They do not inhibit testosterone secretion and are claimed to preserve libido, overall physical performance, and bone mineral density. Although they have not been directly compared in a monotherapy setting, the intensities of pharmacological side effects, gynecomastia, breast pain, and hot flashes appear to be like those of the three available nonsteroidal antiandrogens. However, there are differences in nonpharmacological side effects, with bicalutamide showing a more favorable safety and tolerability profile than nilutamide and flutamide. All three drugs are commonly

hepatotoxic, so liver enzymes must be monitored regularly.[62]

- Flutamide: this study presents the first nonsteroidal antiandrogen available for clinical use. Although it has been studied as a monotherapy for more than 20 years, no dose-finding studies with a currently accepted endpoint have been conducted. It is a prodrug, and the half-life of the active metabolite is 5–6 hours; thus, it must be administered three times a day to maintain therapeutic serum concentrations. The recommended daily dose is 750 mg.[63] Initial phase II trials demonstrated the efficacy of flutamide in the treatment of advanced cancer, although the response rates reported cannot be correlated with currently recommended end points. The main advantage observed in these studies was the preservation of sexual function, which was maintained in 80 % of patients without erectile dysfunction prior to treatment. This finding has not been confirmed in the EORTC 30892 trial, in which only 20 % of men treated with flutamide maintained sexual activity for up to 7 years. The nonpharmacological side effects of flutamide are diarrhea and, occasionally, fatal hepatotoxicity. [64]
- Bicalutamide: in early studies with bicalutamide monotherapy, the 50 mg dose approved for use in total androgen blockade was used. Although bicalutamide 50 mg/day showed beneficial clinical effects, subsequent dose-finding studies revealed that bicalutamide 150 mg once daily achieved a PSA response similar to that of castration while maintaining a good tolerability profile. Therefore, the 150 mg dose was chosen for further evaluation in primary and adjuvant monotherapy.[65] At high doses, it has become an alternative to castration for patients with locally advanced disease (M0), as well as very selected and well-informed cases of M1 stage disease with low PSA.[66] Nonpharmacological side effects include mainly gynecomastia (70 %) and breast pain (68 %), which can be avoided with antiestrogens, prophylactic radiotherapy, or surgical mastectomy. However, bicalutamide clearly offers bone protection compared with LHRH analogs and, probably, LHRH antagonists.[67]
- Estrogens: estrogens have various mechanisms of action: (a) Decreased secretion of gonadotropin-releasing hormone (GnRH); (b) Inactivation of androgens; (c) Direct inhibition of Leydig cell function; (d) Direct cytotoxicity to the prostatic epithelium (in vitro). [52]
- Diethylstilbestrol (DES): initial studies by the Veterans Administration Cooperative Urological Research Group (VACURG) analyzed the use of oral DESs at a dosage of 5 mg/day, as this was the dose used in complete androgen blockade. However, treatment with this dose was associated with high cardiovascular morbidity and mortality due primarily to hepatic metabolism and the formation of thrombogenic metabolites. Consequently, lower oral doses of 1 and 3 mg were analyzed. Both doses provided therapeutic efficacy comparable to that of bilateral orchiectomy, although 3 mg of DES continued to be associated with high cardiotoxicity. However, even though 1 mg of DES had far fewer adverse cardiovascular events than did 5 mg of DES, the side effects of 1 mg of DES remained significantly greater than those of castration. Owing to these problems, as well as the emergence of GnRH agonists and antiandrogens, the use of DESs has been declining for some time because there is currently renewed interest in estrogens.[53]

There are three main reasons for the renewed interest in the use of estrogens to treat prostate cancer.

GnRH agonists have various adverse side effects, and their widespread long-term use is costly, while estrogens inhibit testosterone concentrations without apparently causing bone loss

or cognitive impairment.

Strategies to counteract the cardiotoxicity of estrogen treatment include parenteral administration, which avoids first-pass hepatic metabolism, and the use of cardiovascular protective drugs.

The Scandinavian Prostatic Cancer Group Study 5 was a prospective, randomized trial of more than 900 men with metastatic prostate adenocarcinoma in which parenteral estrogen (polyestradiol phosphate) was compared with total androgen blockade (orchiectomy or GnRH agonist + flutamide). No significant differences in disease-specific survival were observed between the treatment groups, whereas the estrogen-treated group did not show significant increases in cardiovascular mortality. However, the estrogen-treated group had a significantly greater incidence of nonfatal adverse cardiovascular events, particularly ischemic episodes and cardiac decompensation.[56]

In addition, thromboembolic complications were observed in three recent phase II trials of patients with hormone-resistant or advanced prostate cancer. These trials evaluated the combination of DES, 1 or 3 mg/day, with a low dose of warfarin sodium, 1 mg/day, or a low dose of acetylsalicylic acid, 75–100 mg/day, for the prevention of cardiovascular toxicity.

Diethylstilbestrol is one of the classic forms of hormone therapy. Its efficacy was demonstrated many years ago, and a meta-analysis recently reconfirmed that it is like that of bilateral orchiectomy. However, concerns remain about significant cardiovascular side effects, even at lower doses. Further research is needed before estrogen can be readmitted into clinical practice as a standard first-line therapeutic option.[57]

It has been reported that advanced prostate tumors escape androgen blockade through various molecular mechanisms, which tend to make malignant cells independent of the presence of androgens.

Among the molecular escape mechanisms described are the following:

1) Amplification of genes for androgen receptor (AR) expression

2) Selection of androgen receptor mutants that are more efficient at capturing dihydrotestosterone and promiscuous in their interaction with blocking agents (they can act as agonists)

3) Changes in the correlation between the proportions of androgen receptor and its coregulatory molecules, where with minimal presence of the ligand, transcriptional signals are amplified

4) Increased gene expression of hormones for androgen synthesis so that they can be synthesized in situ by malignant cells.

5) Changes in the correlations between the androgen receptor and its coregulatory molecules, including the possibility of signaling to the nucleus via other receptors (illegal pathway), by signaling via the epidermal growth factor receptor (EGFR).

The fifth molecular escape mechanism in prostate tumors, known as the illegal pathway, has a body of clinical evidence. As the tumor becomes more undifferentiated and malignant, cell clones that escape androgen blockade are selected by overexpressing and cosignaling via the epidermal growth factor pathway.[40]

Hormone treatment modalities

Complete hormonal blockade vs. simple hormonal blockade

Complete hormonal blockade involves the addition of a peripheral antiandrogen (flutamide or bicalutamide) to the LHRH analog or surgical castration. The results of this combination are contradictory, although systematic reviews have shown a survival benefit of <5 % with nonsteroidal antiandrogens after 5 years of treatment. In addition, increased costs and increased toxicity are needed. According to the National Comprehensive Cancer Network (NCCN) guidelines, peripheral antiandrogens should be used in conjunction with LHRH analogs from the start of treatment to avoid the "flare effect."

Monotherapy with peripheral antiandrogens

Monotherapy with peripheral antiandrogens can be carried out with bicalutamide at a dose of 150 mg/24 h. Its advantages include the preservation of sexual function and bone mineral density. Its main disadvantages are the onset of gynecomastia and mastodynia in 65 % to 70 % of patients. According to the National Institute for Health and Care Excellence (NICE) guidelines, bicalutamide may be appropriate for patients who accept the problems of this blockade but want to preserve sexual function.

Intermittent androgen deprivation therapy

In the long term, BAC fails to eliminate the entire population of malignant cells. The reason for this is unknown. Therefore, after an average of 24 months, the tumor recurs and returns to a state of androgen-independent growth. Since this progression can begin shortly after the administration of androgen deprivation, coinciding with the cessation of androgen-induced differentiation of progenitor cells, discontinuation of androgen deprivation before the progression of androgen-independent cells would imply that any subsequent tumor growth would be maintained exclusively by the proliferation of androgen-dependent progenitor cells. Thus, progenitor cells should once again be sensitive to androgen deprivation. So-called "intermittent ADT" would thus delay the emergence of the androgen-independent clone. In this way, intermittent ADT reduces the cost and side effects of blockade and potentially delays the onset of castration resistance.

This treatment modality consists of withdrawing ADT and reintroducing it upon evidence of tumor recurrence or progression. It involves close monitoring of the patient through PSA assessment, restarting therapy when PSA levels reach 4–10 ng/ml in nonmetastatic tumors and 10–20 ng/ml in metastatic tumors or upon clinical progression of the disease.

An adequate initial response to ADT is essential and should last at least 6–9 months.

Early blockade vs. late blockade

A particularly controversial aspect of ADT is the timing of treatment initiation, i.e., whether ADT should be started once advanced prostate cancer has been diagnosed or whether, on the contrary, it should be delayed until symptoms or signs of progression are present. There is a lack of high-quality studies comparing the two approaches. Various reviews seem to indicate that, when ADT is started early, it affects disease progression and associated complications rather than overall survival. The main obstacle to its use is its effect on patient morbidity and quality of life, as discussed below. In symptomatic metastatic patients, treatment should be started early to alleviate symptoms and avoid complications such as fractures or spinal cord compression. In asymptomatic or locally advanced metastatic patients, the optimal time to start treatment is not defined, as concluded by the guidelines of the European Society for

Medical Oncology and the American Society of Clinical Oncology.

Progression

Many patients with prostate cancer die from prostate cancer rather than from prostate cancer. The prognosis correlates with the histological grade and extent (stage) of the disease. More than 95 % of prostate cancers are adenocarcinomas and are often multifocal. Localized cancer may be asymptomatic. The average survival rate is five years, and it can take 10 years for metastasis to occur. Currently, the challenge for urologists is early diagnosis, which requires the proactive involvement of general practitioners. The above considerations lead to the conclusion that the clinical expression is diverse, making it essential to enable general practitioners to contribute effectively to prevention and early clinical diagnosis to ensure that patients have a greater chance of being cured and surviving.

Disease progression depends on the stage and grade of the disease at the time of diagnosis. Among M1 patients, only 7 % of patients with metastatic cancer treated with hormone therapy are still alive after 10 years. Survival depends on the PSA concentration at the time of diagnosis, the Gleason score, the volume of metastasis, and the presence of bone symptoms. In patients with locally advanced M0 disease, the median overall survival is often reported to exceed 10 years.

Side effects, quality of life, and cost of hormone therapy

The numerous side effects of long-term androgen deprivation therapy have been well known for years, including the loss of libido, erectile dysfunction, and hot flashes, which are likely the most common side effects. flashes appear 3 months after starting treatment, persist long-term in most patients, and have a significant effect on quality of life. Treatments include hormone therapy and antidepressants.

Some have detrimental effects on quality of life, especially in young men, whereas others may contribute to an increased risk of serious age-related health problems. Many patients for whom such long-term treatment is indicated are still young and physically and sexually active. This is a matter of paramount importance when evaluating various hormone treatment options. Thus, in certain patients, monotherapy with a nonsteroidal antiandrogen (bicalutamide) is becoming increasingly popular because it maintains normal or even high serum testosterone concentrations and has a good tolerability profile.

Before starting long-term treatment, patients should be encouraged to adopt lifestyle modifications, such as increased physical activity, avoidance of toxic habits, and normalization of body mass index. An accurate assessment of BMD should be performed via dual-energy X-ray absorptiometry at baseline. A low initial BMD (T score above 2.5 or above 1 when other risk factors are present) indicates a high risk of subsequent nonmetastatic fracture, indicating the need for early use of preventive treatment with bisphosphonates.

There is an increased risk of nonmetastatic bone fractures because of increased bone turnover and a time-dependent reduction in bone mineral density (BMD). This represents an increase in fracture risk of up to 45 % in terms of long-term relative risk. This is a significant side effect, as hip fractures in men carry a significant risk of mortality. Increased exercise and calcium supplements are protective.

It has recently been shown that bisphosphonates, such as pamidronate, alendronate, or

zoledronic acid, increase bone mineral density in the hip and spine by up to 7 % in one year. The optimal zoledronic acid regimen is unclear. One study recommended treatment every 3 weeks, whereas another trial reported similar results, with one injection per year. The optimal regimen is very important because of the risk of jaw necrosis, which may be related to dose and timing. Baseline BMD can be used to guide the choice of regimen. Therefore, quarterly injections could be used in patients with osteoporosis, in whom an annual injection is likely to offer insufficient protection.

An important advance in bone protection is the introduction of Denosumab, a fully human monoclonal antibody that is an essential mediator of osteoclast function, activation, and survival. Its beneficial effect is not associated with significant toxicity, with no osteonecrosis of the jaw or delay in the healing of vertebral fractures. Therefore, this compound could represent a significant improvement in bone protection.

Obesity and sarcopenia are common and often appear early, during the first year of treatment. There is an expected increase in body fat mass of up to 10 % and a reduction in lean tissue mass of up to 3 %. Both changes are associated with an increased risk of fracture.

Lipid abnormalities are also common and appear within the first 3 months of treatment. It also reduces insulin sensitivity and increases the fasting plasma insulin concentration, which is a marker of insulin resistance. Exercise should be recommended as a protective measure. Metabolic syndrome is associated with independent cardiovascular risk factors, often accompanied by insulin resistance.

It has been associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction, as well as a 20 % increase in the risk of new cardiovascular events after one year of treatment.

Follow-up methods

Prostate-specific antigen monitoring

PSA is a good marker for monitoring the progression of metastatic prostate cancer. The prognostic value of the PSA level, which is based on the value prior to initial treatment or on the reduction in the PSA level during the first three to six months, has been used to monitor cancer incidence in recent decades. The initial PSA concentration reflects the extent of metastatic disease, although some poorly differentiated tumors do not secrete PSA. The prognostic utility of the pretreatment PSA value has been evaluated variably in the literature and should not be used solely to predict the duration of response to treatment. After the initial phase of response to hormone therapy, patients should be monitored periodically to detect and treat possible complications of endocrine escape, as clinical progression of the disease occurs after a median of 12–18 months of treatment in patients with M1-stage tumors. Regular PSA monitoring in asymptomatic patients has been shown to allow earlier detection of biochemical escape, as elevated PSA levels usually precede the onset of clinical symptoms by several months. However, it should be noted that PSA levels are not a reliable marker of escape and cannot be used alone as a follow-up test. Clinical disease progression (bone pain) has been reported with normal PSA levels.

Monitoring creatinine, hemoglobin, and liver function

Creatinine monitoring is useful because it can detect upper urinary tract obstruction in patients with advanced cancer who may need relief through percutaneous nephrostomy or

double J stenting. Hemoglobin and liver function tests may indicate disease progression or hormone therapy toxicity (hepatotoxicity from nonsteroidal antiandrogens), which may lead to discontinuation of treatment. Notably, hemoglobin levels decrease by 20 % with androgen deprivation. Alkaline phosphatase and its bone-specific isoenzymes can be used to monitor patients with M1b disease. These markers have the advantage of not being directly influenced by hormone therapy, unlike PSA. Notably, increased serum alkaline phosphatase concentrations may also be due to osteoporosis induced by androgen deprivation. In this situation, the determination of bone-specific alkaline phosphatase may be useful.

Bone scan, ultrasound, chest X-ray, CT scan, and SPECT/CT

In routine practice, asymptomatic patients with normal PSA levels should not undergo bone scans at regular intervals, as disease progression is detected more reliably by PSA measurement in conjunction with other tests and is also less costly. In addition, the interpretation of bone scans is sometimes difficult, and the appearance of a new focus of uptake or the deterioration of preexisting lesions in an asymptomatic patient does not change the therapeutic strategy. In cases where there is clinical or analytical suspicion of disease progression, a chest X-ray or renal and hepatic ultrasound may be indicated. Imaging techniques should also be guided by symptoms. However, the systematic use of these tests in asymptomatic patients is not recommended.

Testosterone Control

Most patients with prostate cancer treated with LHRH analogs achieve serum testosterone levels equal to or below the castration concentration (< 20 ng/dl). However, approximately 13–38 % do not achieve this therapeutic goal, whereas 2–17 % do not achieve a serum testosterone concentration less than 50 ng/dl. In addition, some patients experience testosterone spikes during long-term treatment with agonist readministration, which is described as an acute-on-chronic effect. Testosterone spikes can also be observed at any time during treatment, which is called an intercurrent response; they can occur in 2–13 % of patients treated with LHRH agonists. There is limited information about the optimal testosterone concentration that needs to be achieved in the treatment of prostate cancer. Recent studies have indicated that lower testosterone concentrations may be associated with better outcomes.

In view of these results, the determination of the serum testosterone concentration, as well as the serum PSA concentration, should be part of clinical practice in men receiving LHRH treatment. The timing of testosterone measurements is not clearly defined. The first assessment of testosterone concentration may be recommended one month after starting LHRH treatment to determine the testosterone nadir achieved before the agonist is readministered. An assessment of testosterone concentration may be performed at 6 months to evaluate the efficacy of treatment and ensure that the castration concentration is maintained. If not, switching to another LHRH-acting drug or surgical orchiectomy may be attempted. In patients with increased PSA or clinical signs of progression, the testosterone concentration should be assessed in all cases to confirm castration resistance.

Management of metabolic complications.

The most common side effects of low testosterone levels include hot flashes, lack of libido, erectile dysfunction, gynecomastia, and loss of bone mineral density. However, recent studies have also shown that men with low testosterone concentrations have a greater incidence of metabolic complications, such as insulin resistance, arterial stiffness, diabetes, and metabolic syndrome. Metabolic syndrome is present in more than 50 % of patients receiving long-term

androgen deprivation therapy, predisposing them to increased cardiovascular risk and a higher likelihood of dying from coronary heart disease and other cardiovascular diseases, which have become the most common cause of death in these patients, surpassing even mortality from prostate cancer. A cardiology consultation may be beneficial in patients with a history of cardiovascular disease and in those over 65 years of age before starting treatment. All patients underwent diabetes screening by measuring fasting blood glucose and HbA1c (at baseline and then every 3 months). In certain cases, a glucose tolerance test may be necessary. Men with impaired glucose tolerance or diabetes should undergo an endocrinological consultation. Patients treated with TPA should receive advice on lifestyle changes (diet, exercise, smoking cessation, etc.) and be treated for any preexisting conditions, such as diabetes, hyperlipidemia, or hypertension.

Monitoring fasting glucose levels, lipid profiles, and blood pressure is recommended for all patients treated with long-term total androgen deprivation (TAD). The risk–benefit ratio of TAD should be considered in patients at greater risk of cardiovascular complications, especially when it is possible to delay the start of treatment.

When the goal is to increase the life expectancy of men with the highest quality of life, this disease presents itself as a health problem for our society.

Prostate cancer is a major problem, and different strategies for the management and treatment of patients suffering from this disease have been proposed and implemented around the world, with unanimous agreement on the curability of early-stage disease (T_1, T_2, N_0, $_{and}$ M0), with therapeutic variants of proven effectiveness for advanced cancer.

Specifically, at Joaquín Albarrán Hospital, after the biopsy results, we make an initial classification on the basis of the PSA at diagnosis and the Gleason score and group, and treatment begins with total androgen blockade via oral antiandrogens (bicalutamide or flutamide) and LH–RH analogs (goserelin), indicating staging consisting of hematological studies (complete blood count, blood chemistry including renal function, liver function, and alkaline phosphatase), abdominal and renal ultrasound, transrectal or abdominal prostate ultrasound, chest X-ray, and bone scan. A CT or PET/CT scan was indicated if the above studies were inconclusive.

Patients over 75 years of age are indicated for the same studies, but treatment starts with diethylstilbestrol at a loading dose of 15 mg daily for 15 days and then continues with 1 mg daily associated with aspirin (125 mg). If cardiovascular risk contraindicates medication, surgical castration is performed. This surgery will be offered to all patients over 75 years of age who are resistant to castration, and whether it is performed will depend on their acceptance.

If the stage is negative, regardless of the risk, the patient is referred to oncology for evaluation of radiotherapy in stages T1, T2, and T3, N0, and M0, associated with neoadjuvant therapy with total androgen blockade, which will be maintained for up to 2 years after completion of the therapy; these patients will then be placed under active surveillance.

At the hospital, we do not have previous studies on the behavior of prostate adenocarcinoma, which is the first to provide better monitoring and detect deficiencies in the treatment and follow-up of this pathology with the aim of solving the problems that arise to comply with the requirements of preventive medicine.

Currently, our service has seen an increase in patients with signs of progression, considering the elevation of PSA levels after an initial positive response, elevation of liver function tests, ureterohydronephrosis, lymphedema, hepatomegaly, and lymph node, respiratory and bone manifestations, which are revealed in the annual follow-up. This leads to disease progression or hormone resistance, so we opt for new therapeutic approaches to improve quality of life.

Patients with bone metastases are referred to oncology for chemotherapy consisting of zoledronic acid in monthly cycles of 6 and 12. Patients with liver or lymph node metastases receive docetaxel and prednisone as second-line treatment, and total androgen blockade, which is interrupted in the event of hematological alterations, is maintained.

Chapter 04 / Capítulo 04

Advanced Prostate Adenocarcinoma and Androgen Deprivation Therapy. Clinical Outcomes, Risk Stratification, and Therapeutic Results
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Field study: design, criteria, variables, and instruments

Study design and methodological framework

The empirical analysis developed in this volume was based on a descriptive observational study structured under a cross-sectional design. This approach allowed us to examine the clinical behavior of patients diagnosed with advanced prostate adenocarcinoma who were undergoing total androgen deprivation and were treated at the Urology Department of the Joaquín Albarrán Domínguez Clinical Surgical Teaching Hospital during an observational period of several years.

The choice of an observational design corresponded to the nature of the phenomenon studied. The central interest was not to intervene in therapeutic variables but to describe clinical patterns, evolutionary trajectories, and diagnostic characteristics as they manifested themselves in routine healthcare practice. The descriptive nature of the study allowed us to characterize the expression of the variables of interest within the defined institutional context, preserving the complexity inherent in the real clinical environment.

The cross-sectional design facilitated the integration of clinical information corresponding to a defined time interval, offering a structured view of patient evolution under comparable therapeutic conditions. This approach made it possible to examine biochemical indicators, clinical parameters, and functional dimensions relevant to the follow-up of advanced prostate cancer patients.

Study population

The reference population consisted of all patients diagnosed with prostate adenocarcinoma treated at the hospital during the period analyzed. A total of 234 patients with a confirmed diagnosis of prostate adenocarcinoma were identified during an observational period of several years.

This population included patients with different stages of the disease, diverse clinical trajectories, and heterogeneous therapeutic regimens. From this group, a specific sample was selected, aimed at capturing only those cases that met clinical and therapeutic characteristics compatible with the study objectives.

Sample selection

The final sample consisted of 73 patients who met the previously defined selection criteria. This process allowed us to define a homogeneous group in terms of age, clinical stage, and therapeutic strategy, favoring the analytical consistency of the study.

The definition of the sample corresponded to the need to examine the behavior of advanced prostate adenocarcinoma under a specific therapeutic regimen: total androgen deprivation. This selection reduced the variability derived from alternative treatments or noncomparable clinical stages.

Inclusion criteria

Patients over 50 years of age with a confirmed diagnosis of advanced prostate adenocarcinoma were included in the study. Similarly, only those individuals who were undergoing clinical follow-up through the outpatient clinic of the Joaquín Albarrán Domínguez Hospital and who had received treatment based on total androgen blockade were considered.

The inclusion of patients in outpatient follow-up ensured the availability of systematic clinical information, serial biochemical parameters, and consistent evolutionary evaluation. Therapeutic homogeneity allows for the analysis of clinical response within a comparable hormonal intervention framework.

Exclusion criteria

Patients with a history of autoimmune diseases, previous malignant neoplasms, or prostate diagnoses other than invasive adenocarcinoma, such as prostatic intraepithelial neoplasia or focal glandular atypia, were excluded. This decision was made to avoid potential confounding factors that could interfere with the interpretation of clinical progression or response to hormone therapy.

Likewise, patients with neurological or psychological conditions that prevented adequate understanding or response to the clinical assessment instruments used were not included. This criterion preserved the consistency of the information obtained, particularly in relation to functional and quality of life variables.

Methods, techniques, and procedures for obtaining information.

To achieve the proposed objectives, information was collected through statistical records, medical records, and pathological anatomy reports, which were compiled in the data collection form (Appendix I), where all the variables of interest for the research were recorded.

With the information provided in the instrument, we classify patients by risk, which is very low, low, intermediate favorable and unfavorable, high, and very high, in addition to identifying the stage of their disease at the time of diagnosis and when it progresses to advanced stages, thus forming the sample to be used in our research. We based our classification on PSA levels, Gleason score, histopathological grade, digital rectal examination, abdominal and bladder-prostate ultrasound, complete blood count, and blood chemistry. Through the histological study of the Trucut biopsy, we were unable to stage patients in T3 and T4, as the sample size was insufficient for analysis. However, in the presence of stony, fixed, asymmetrical prostates with irregular edges or upon physical examination of lymphedema in the lower limbs due to the presence of inguinal adenopathies, as well as ultrasound findings of ureterohydronephrosis secondary to trigone infiltration, these findings were characteristic of stages T3 and T4.

Written informed consent was obtained from the patients to participate in the study, and each participant was interviewed to explain the principles of treatment, follow-up, and symptoms for better identification of recurrence. The health status of the participants after the start of anti-androgen treatment was investigated, with reference to symptoms such as decreased sexual desire, hot flashes, bone pain, gynecomastia, and mastodynia. In addition, the progression of the stages was monitored via review and detection of increases in PSA, alterations in testosterone, the appearance of bone metastases, and physical examination to detect the presence of lymphedema and inguinal adenopathies.

Table 4.1 shows the operationalization of the variables. For each variable, the definition and scales are presented to facilitate understanding of the analysis.

Table 4.1. Operationalization of variables

Variable	Definition	Scale used
Age	Years of age at the start of the study were considered, grouped by category	Less than 50 50-54 55-59 60-64 65-69 70 and over
Total androgen blockade	- Patients who are unlikely to undergo surgery or those who refuse surgery. - Patients who have undergone surgery	Pharmacological Surgical
Appearance of signs of progression	Depending on the appearance of signs of progression in patients	Local invasion Distant metastasis Hormone resistance
Prostate Surface Antigen	Prognostic parameter to establish treatment effectiveness, at the time of diagnosis and every 3 months	According to patient values. < 4 ng/ml in metastatic disease <0,5 ng/ml in controlled disease.
Testosterone	Prognostic parameter to establish treatment effectiveness, depending on castration concentration. Hormone resistance	According to patient values. Normal value: < 20 ng/dl
Hemoglobin	Prognostic parameter for establishing treatment effectiveness	According to patient values. Normal value: < 13 g/l
Creatinine	Prognostic parameter for establishing treatment effectiveness depending on renal function	Based on patient values. Normal value: < 113 mmol/L
Liver enzymes	Prognostic parameter for establishing treatment effectiveness depending on liver function	According to patient values. Normal value: Glutamic pyruvic transaminase. 5-40 U/L (GPT or ALT) Glutamic oxaloacetic transaminase. 7-56 U/L (GOT or AST)
Degree of cellular differentiation	Histological study result	Differentiated Moderately differentiated Undifferentiated
Gleason classification	Assigning a score based on greater or lesser differentiation and glandular histology	From 1 to 10
Risk classification	Based on physical examination, histological results, and complementary tests	Low Very low Favorable intermediate Intermediate unfavorable High

Bioethical considerations

During this research, the standards for medical research involving humans established in the Declaration of Helsinki were followed, which set out four basic ethical principles: respect for

persons, beneficence, nonmaleficence, and justice.

This research was endorsed by the Research Ethics Committee and the Scientific Council of the Joaquín Albarrán Domínguez Clinical-Surgical Teaching Hospital.

The surveys were anonymous and were administered after informed consent was obtained, making it clear that the respondents' data would not be disclosed to third parties and would only be handled by the research participants, who undertook not to disclose any data that would allow the respondents to be identified.

The results of the evaluation of the instruments were collected in a database, which was kept under the care of the person responsible for the research.

Each patient was asked to participate after the objectives of the study and the procedures that would be followed if they agreed to collaborate were explained. They were told that they were completely free to refuse to participate, without any consequences for their present and/or future medical care, as this was their right. This was done in conjunction with the informed consent document, and only if they agreed to participate in the research did they sign it as proof of their desire to do so.

Chapter 05 / Capítulo 05

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Study results

Age distribution and risk classification

The distribution of patients by age group clearly showed a pattern of concentration in older age groups. The largest proportion of the cohort was in the over70 years of age group, which was the most represented age segment in the analyzed group.

When the risk classification was examined simultaneously, this age predominance remained consistent both in patients categorized as high risk and in those classified within the very high-risk group. In both cases, individuals over 70 years of age represented more than half of the patients included in each category.

The younger age groups showed considerably lower participation. The 50–59 years age group accounted for a small fraction of the total cases, whereas patients between 60 and 70 years of age were moderately represented, although not to the same extent as the older age group.

From a clinical perspective, this distribution is consistent with the epidemiological behavior of prostate adenocarcinoma, whose incidence increases progressively with age. The accumulation of cases in advanced stages of life can be linked both to the natural history of the disease and to diagnostic detection patterns.

Similarly, the high proportion of high- and very high-risk patients in the older age groups suggests a possible association between age at diagnosis and clinical aggressiveness. This finding reinforces the importance of timely detection strategies, systematic follow-up, and adequate risk stratification in aging populations.

Table 5.1. Distribution of patients according to age group and risk classification

Age	High		Very High		Total
	No	%	No	%	
50 to 54 years old	1	3	1	3	2
55 to 59 years old	3	9	4	9	7
60 to 65 years old	5	15	5	12	10
66 to 70 years old	4	12	7	18	11
>70 years old	20	61	23	58	43
Total	33	100	40	100	73

Adherence to treatment throughout the observation period

The analysis of therapeutic adherence showed variations throughout the different time points considered within the observation period. In general, most patients adhered to the indicated treatment, suggesting sustained acceptance of the total androgen deprivation strategy within the analyzed cohort.

However, when the distribution according to the different time points of follow-up was examined, relevant differences emerged. The late intermediate phase had the highest frequency of nonadherent cases, representing the interval in which this condition reached its highest expression. This behavior contrasted with that observed at the beginning of the period and in the early intermediate phase, stages in which adherence was the clearly predominant pattern.

During the beginning of the period, episodes of interruption or noncompliance with therapy were recorded in a reduced proportion, reflecting relative stability in treatment continuity. Similarly, in the early intermediate phase, adherence remained predominant, suggesting initial consolidation of the therapeutic regimen within the healthcare dynamic.

In the late intermediate phase, however, there was a noticeable increase in nonadherence. This variation could be linked to multiple clinical and contextual factors, including the cumulative onset of adverse effects, changes in the subjective perception of therapeutic benefit, difficulties in accessing medication, or changes in patients' personal and social circumstances.

Toward the end of the period, although cases of nonadherence persisted, their magnitude was lower than that recorded in the late intermediate phase. This behavior suggests a partial reduction in the variability observed previously, although without fully returning to the levels of adherence predominant in the initial stages.

From a clinical perspective, these fluctuations underscore the dynamic nature of therapeutic adherence in prolonged hormone treatments. The continuity of total androgen blockade does not depend exclusively on medical indications but also on individual tolerance, the subjective experience of treatment, and sustained interaction between the patient and the healthcare system.

Likewise, the identification of a phase with a higher frequency of nonadherence invites consideration of the possible influence of organizational, care, or psychosocial factors that may have affected this behavior. Adherence, especially in the context of chronic oncological diseases, is an essential component not only of therapeutic effectiveness but also of patient evolutionary stability.

Finally, nonadherence should not be interpreted solely as isolated individual behavior. It often reflects complex interactions between treatment characteristics, clinical conditions, perceptions of side effects, institutional support, and patients' life circumstances.

Therapeutic adherence according to time during the observation period

The distribution of treatment adherence varied among the different time points considered within the observation period. In general, adherence remained the predominant pattern at all stages of follow-up, although there were noticeable differences in the magnitude of nonadherence.

Table 5.2. Distribution of patients according to treatment adherence

Time of the period	Adherence	Nonadherence	Total
Start of period	16	1	17
Early intermediate stage	19	2	21
Late intermediate stage	14	7	21
End of period	10	4	14

During the beginning of the period, cases of nonadherence were rare, suggesting initial stability in treatment continuity. In the early intermediate phase, this behavior continued, with only a small proportion of patients interrupting or not adequately complying with the therapeutic regimen.

The late intermediate phase had the highest frequency of nonadherence, representing the moment of greatest variability within the series analyzed. At this stage, the highest number of patients who did not maintain therapeutic continuity was observed, suggesting the possible influence of clinical, pharmacological, or contextual factors that could have affected adherence.

Toward the end of the period, although episodes of nonadherence persisted, their frequency was lower than that recorded in the late intermediate phase. This behavior indicates a partial reduction in the variability observed previously, without fully reaching the levels of stability present in the initial stages.

From a clinical perspective, these fluctuations reinforce the dynamic nature of adherence to prolonged hormone treatments. The continuity of total androgen blockade may be influenced by the appearance of adverse effects, the subjective perception of benefit, individual tolerance to treatment, and conditions of access and follow-up care.

Clinical evolution according to initial risk classification

Analysis of the evolution of patients toward high-risk categories allowed us to identify relevant differences on the basis of initial stratification. The observed distribution revealed that progression toward more clinically aggressive states did not occur uniformly across the different risk groups.

Patients initially classified in the unfavorable intermediate-risk group constituted the segment with the highest proportion of progression to high risk. This pattern suggests that, within this category, the disease showed a greater tendency to present signs of progression or clinical restratification during follow-up.

Similarly, although to a lesser extent, individuals belonging to the favorable intermediate-risk group also showed a significant proportion of progression to higher-risk categories. This finding is of particular clinical interest, as it highlights that even within classifications considered relatively more stable, less favorable evolutionary trajectories can be recorded.

In contrast, patients in the low- and very low-risk groups presented the lowest frequencies of progression to high risk. This behavior suggests greater clinical stability within these categories, which is consistent with the prognostic profile generally associated with these classifications.

From an analytical perspective, the difference observed between the favorable and unfavorable intermediate groups reinforces the relevance of substratification within intermediate risk. This group, which is far from constituting a uniform category, brings together patients with potentially divergent trajectories, underscoring the need for differentiated clinical surveillance.

The progression to high risk not only implies a change in prognostic categorization but also may translate into modifications in therapeutic strategy, follow-up intensity, and the evaluation of progression markers. In this context, the identification of transition patterns has both clinical and organizational value.

Furthermore, these results invite reflection on the biological dynamics of advanced prostate adenocarcinoma. Disease progression may involve multiple mechanisms, including variations in hormonal sensitivity, tumor heterogeneity, the emergence of resistant clones, and individual host factors.

Finally, the lower proportion of progression observed in the low- and very low-risk groups does not exclude the possibility of progression but suggests more stable trajectories within the period analyzed. This finding reaffirms the importance of initial risk classification as a fundamental tool in predicting progression and planning clinical management.

Table 5.3. Distribution of patients according to progression to high risk by risk classification

Risk	No	High risk	%
Very low	57	10	13,7
Low	31	9	12,3
Favorable intermediate	33	12	16,4
Unfavorable intermediate	40	22	30,1
Subtotal	161	53	72,6
Total High Risk		73	

Clinical progression and time of onset of manifestations

Analysis of the relationship between treatment time and clinical signs associated with disease progression revealed distinct patterns in the presentation of complications.

Table 5.4. Correlation between signs of progression and time of onset

Treatment time	Bone metastases		Lymphadenopathy		Renal failure		Total
	No	%	No	%	No	%	
1 year	9	39,1	4	17,4	0	0,0	23
2 years	8	40,0	3	15,0	2	10,0	20
3 years	19	76,0	3	12,0	0	0,0	25
Total	36	49,3	10	13,7	2	2,7	73

Bone metastases were the most frequent manifestation of clinical progression within the evaluated cohort. Approximately half of the patients developed bone involvement during follow-up, confirming the predominant role of the skeleton as a common site of progression in advanced prostate adenocarcinoma.

When the time of onset was examined, the highest proportion of bone metastases was recorded in patients with longer treatment times. This behavior suggests a progressive accumulation of the risk of bone dissemination as the clinical course of the disease under total androgen deprivation is prolonged.

Lymphadenopathy, although present in a relatively small proportion of patients, represents another relevant form of progression. Its distribution was relatively stable between the different treatment intervals, without evidence of a pattern of concentration as marked as that observed in bone metastases.

Renal failure occurred in a small number of patients. This low frequency suggests that, within the group analyzed, renal involvement associated with tumor progression was a less common event. However, its clinical relevance is significant because of its potential impact on prognosis, quality of life, and the complexity of therapeutic management.

From a clinical perspective, these findings reflect the heterogeneity in the evolutionary

trajectories of advanced prostate adenocarcinoma. Progression does not manifest uniformly but rather takes on diverse clinical expressions that are influenced by biological factors, tumor characteristics, response to hormonal treatment, and individual patient conditions.

The predominance of bone metastases as the main sign of progression reaffirms the importance of systematic monitoring of skeletal involvement during follow-up. Timely detection of this manifestation is essential for adjusting therapeutic strategies, preventing related skeletal events, and optimizing symptom control.

Likewise, the appearance of adenopathy and, to a lesser extent, renal failure underscore the need for a comprehensive evaluation that considers both locoregional progression and possible systemic complications.

Time of onset of hormone resistance

Analysis of the timing of hormone resistance revealed different patterns depending on the duration of treatment and the biochemical markers evaluated. The transition to hormone escape states was not uniform but showed significant variations between the different follow-up intervals.

In the earliest phases of treatment, particularly during the first few months, the identification of signs compatible with hormone resistance was limited. Elevated prostate-specific antigen (PSA) levels were detected in a small number of patients, whereas no significant increases in testosterone levels were detected.

As the treatment time increased, a progressive increase in the frequency of biochemical alterations was observed. During the first year of follow-up, elevated PSA emerged as the predominant finding, suggesting residual tumor activity or disease reactivation in a considerable group of patients.

At later intervals, the distribution of the markers substantially changed. Elevated testosterone became more relevant in patients with longer treatment durations, reaching its maximum expression in those with longer treatment durations. This behavior suggests an association between the duration of androgen blockade and the appearance of hormonal escape mechanisms.

The predominance of elevated testosterone in later stages reinforces its role as a critical parameter in identifying hormone resistance. The recovery or increase in serum testosterone levels may reflect a loss of effective androgen suppression, a phenomenon closely linked to the biological progression of the tumor.

PSA elevation, which is observed more frequently in intermediate phases of treatment, is an early indicator of possible tumor reactivation. Its dynamic behavior during follow-up allows changes in disease activity to be detected before the onset of obvious clinical manifestations.

From a clinical perspective, these findings underscore the importance of joint monitoring of PSA and testosterone in patients undergoing total androgen deprivation. The integrated interpretation of both markers allows for a more accurate assessment of therapeutic response and detection of hormonal escape states.

Likewise, the variability in the timing of hormone resistance onset reflects the biological complexity of advanced prostate adenocarcinoma. Intrinsic tumor factors, cellular heterogeneity, clonal adaptation, and differential sensitivity to hormone suppression may contribute to explaining these evolutionary trajectories.

Table 5.5. Distribution of patients according to the timing of hormone resistance onset

Treatment time	PSA elevation		Elevation of testosterone		Total
	No	%	No	%	
6 months	5	10,0	0	0,0	5
1 year	10	52,6	9	47,4	19
2 years	7	46,7	8	53,3	15
3 years	3	13,6	19	86,4	22
Total	25	41,0	36	59,0	61

Behavior of the metastatic lesions

Analysis of the behavior of the metastatic lesions allowed us to characterize the clinical evolution of patients who presented with bone involvement during follow-up. Within this group, a significant proportion of patients received treatment with zoledronic acid as part of the therapeutic strategy aimed at controlling skeletal complications.

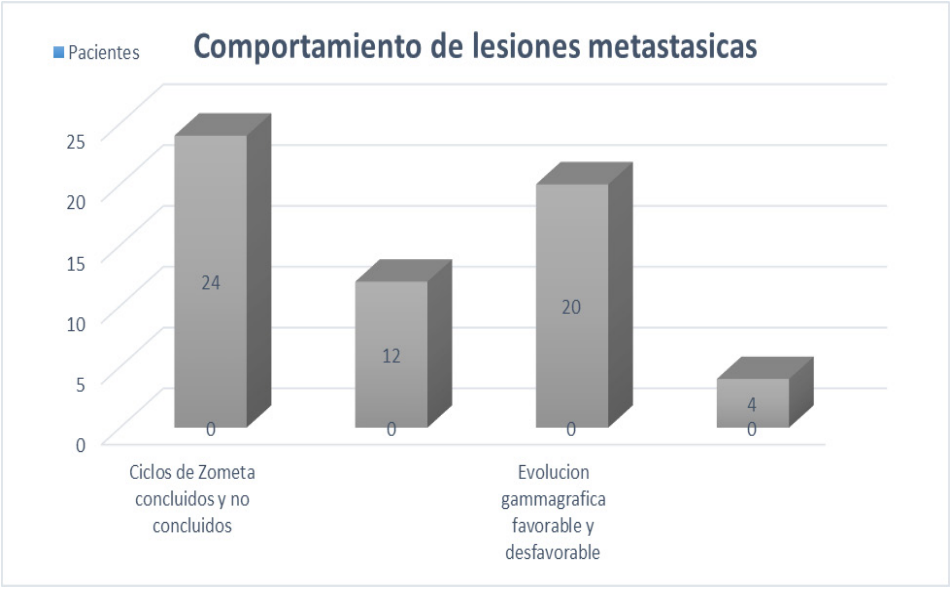

Figure 5.1. Distribution of patients according to metastatic lesions

The distribution revealed that most patients who started treatment with zoledronic acid were able to complete it, suggesting adequate tolerability and therapeutic continuity in a considerable number of cases. This finding is relevant in the context of the management of advanced prostate adenocarcinoma, where adherence to complementary therapies is crucial for the prevention of related bone events.

Scintigraphic follow-up allowed for the evaluation of the structural response of the metastatic lesions. In a significant proportion of patients, improvements in previously identified alterations were observed, suggesting a favorable effect of the therapeutic approach on skeletal disease activity.

However, the evolution was not uniform in all the cases. The coexistence of favorable and unfavorable trajectories reflects the biological complexity of metastatic disease, as well as the influence of individual factors, tumor burden, hormonal response, and the characteristics of systemic treatment.

From a clinical perspective, the scintigraphic improvement observed in a group of patients supports the relevance of using antiresorptive agents in the comprehensive management of advanced prostate cancer with bone involvement. Stabilization or reduction of metastatic activity can translate into functional benefits, pain reduction, and better control of skeletal complications.

Likewise, the need to complete therapeutic cycles highlights the importance of systematic follow-up, evaluation of adverse effects, and adherence to treatment as central components of clinical effectiveness.

Impact of androgen deprivation on health status

The evaluation of the clinical impact associated with androgen deprivation revealed a variety of manifestations perceived by patients during treatment. The distribution of the events described showed that alterations in sexual function were the most frequent expression within the cohort analyzed.

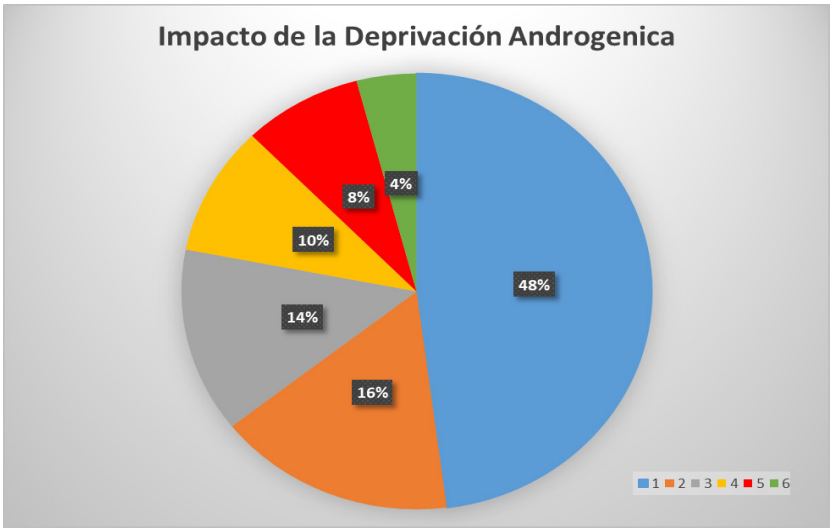

Figure 5.2. Impact of androgen deprivation on health status
Note: 1. Sexual dysfunction 2. Gynecomastia 3. Mastodynia; 4. flashes 5. Bone pain; 6. Hepatotoxicity

Sexual dysfunction emerged as the predominant adverse effect, accounting for the highest proportion of responses. This finding is consistent with the mechanism of action of androgen blockade, whose interference with testosterone production and activity directly affects erectile

function, libido, and the overall sexual response.

To a lesser extent, patients reported vasomotor symptoms, particularly hot flashes, a widely recognized manifestation in the context of hormonal suppression. Although their frequency was lower than that of sexual dysfunction, their subjective impact can be significant because of their recurrent nature and potential interference with daily well-being.

Other events, such as gynecomastia and mastodynia, have also been reported, reflecting alterations related to the hormonal imbalance induced by therapy. These manifestations, even when they occur in a smaller proportion of patients, can cause physical discomfort and psychological repercussions in certain patients.

Bone pain was reported in a small fraction of the sample. This symptom may be linked to both the systemic effects of treatment and the natural progression of the disease, particularly in patients with skeletal metastatic involvement.

Hepatotoxicity, identified in a limited number of cases, was the least frequent manifestation. Despite its low relative incidence, its clinical relevance is considerable, as it may require therapeutic adjustments, modifications to the pharmacological regimen, or specialized follow-up interventions.

From a comprehensive clinical perspective, these findings underscore that androgen deprivation, although essential in the control of advanced prostate adenocarcinoma, is associated with adverse effects that transcend the strictly oncological dimension. The patient's therapeutic experience involves physical, functional, and psychosocial components that require systematic evaluation.

Similarly, the high frequency of sexual dysfunction highlights the need to incorporate clinical support strategies, therapeutic guidance, and an interdisciplinary approach focused on quality of life.

Partial conclusions of the chapter

The findings presented in this chapter allow us to perform a comprehensive characterization of the clinical and evolutionary behavior of patients diagnosed with advanced prostate adenocarcinoma who are undergoing total androgen deprivation.

The age distribution clearly revealed a predominance of older patients, a pattern consistent with the known epidemiology of the disease. This concentration in older age groups not only reflects demographic trends but also introduces relevant clinical considerations in terms of comorbidities, therapeutic tolerance, and functional vulnerability.

Analysis of therapeutic adherence revealed that although treatment continuity remained the predominant behavior, there were fluctuations between different points in the observation period. The identification of a phase with increased nonadherence underscores the dynamic nature of this phenomenon and its possible link to clinical factors, adverse effects, the subjective perception of treatment, and contextual conditions.

In relation to clinical progression, bone metastases have emerged as the most frequent manifestation of disease progression. This finding reaffirms the central role of skeletal

involvement in the natural history of advanced prostate adenocarcinoma and highlights the importance of therapeutic strategies aimed at its control and monitoring.

The evaluation of the timing of hormone resistance revealed different patterns among the biochemical markers analyzed. Elevated PSA was more frequently observed in the intermediate stages of follow-up, whereas elevated testosterone became more prominent in the later stages of treatment. This behavior reflects the biological complexity of hormonal escape and the need for integrated monitoring of both indicators.

The clinical impact associated with androgen deprivation revealed that sexual dysfunction was the most frequently reported manifestation among patients. This result highlights that, along with oncological control, the therapeutic experience involves functional and psychosocial dimensions that directly affect quality of life.

Taken together, the findings described here reveal that the evolution of advanced prostate adenocarcinoma under total androgen blockade is a heterogeneous process influenced by complex interactions between clinical, biochemical, and therapeutic variables. This heterogeneity requires individualized follow-up approaches, systematic evaluation of progression markers, and clinical care that integrates both the biological dimension of the disease and the patient's experience.

The analysis developed in this chapter thus lays the groundwork for the critical interpretation of the results, addressed in subsequent chapters, which delve into the clinical, therapeutic, and healthcare implications derived from these findings.

Chapter 06 / Capítulo 06

Advanced Prostate Adenocarcinoma and Androgen Deprivation Therapy. Clinical Outcomes, Risk Stratification, and Therapeutic Results
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Clinical discussion and implications

Prostate cancer is a hormone-dependent neoplasm with significant heterogeneity. Clinical behavior, response to treatment, and survival vary depending on the patient. More than 95 % of prostate cancers are adenocarcinomas. The risk of prostate adenocarcinoma increases with age, especially after 50 years, but more than 80 % of patients over 65 years of age are diagnosed with prostate adenocarcinoma. In a study of progression according to the type of treatment applied, published in the Spanish Urological Journal, the average age was 74,33 years. A case–control study on prostate cancer risk factors conducted by the National Institute of Oncology and Radiobiology in 2015 revealed that patients aged 65--84 years accounted for 89 % of the cases related to population aging. The results of this research coincide, with the over70 years of age group having a 61 % high risk and 58 % very high risk.[69]

A lack of adherence to treatment in the context of oncological diseases is considered a serious health problem. It is a very complex process that requires education and support for the patient to achieve active and responsible participation in treatment. Nonadherence to treatment in 2019 was more representative, with seven patients due to instability in the supply of pharmacological treatment to the center, followed by 2020, where the epidemiological situation had an impact, with a decrease in attendance at follow-up appointments and medication collection.

Currently, most prostate cancer cases are diagnosed in the early stages, whereas only 5–10 % are diagnosed at advanced stages. The biological and clinical progression rates of T1 and T2 prostate adenocarcinomas are 11,36 % and 9,09 %, respectively.[70]

During the study, depending on the risk classification, progression to advanced stages occurred in 13,7 % and 12,3 % of very low-risk and low-risk patients, respectively. Moreover, 34 patients at intermediate risk progressed.

Bone metastases were the most frequent sign of disease progression in the present study, accounting for 49,3 %, with the highest incidence occurring at 3 years. A total of 10 patients developed lymphadenopathy, with the highest incidence occurring one year after treatment. Renal failure occurred in a total of 2 patients, accounting for 10 % of the total.

Hormone-sensitive advanced prostate cancer accounts for approximately 3 % of prostate cancer cases in the US, approximately 6 % in Europe, nearly 60 % in the Asia-Pacific region, and approximately 40 % in Latin America, and its incidence is increasing.

Although patients generally respond initially to androgen deprivation therapy, most progress to hormone resistance within 12–15 months. After hormone therapy, a reduction in PSA to undetectable concentrations provides information regarding the duration of disease progression-free status; however, a decrease in PSA to less than 80 % may not be very predictive. Because PSA expression itself is under hormonal control, androgen deprivation therapy can decrease the serum PSA concentration regardless of the tumor response. Consequently, the serum concentration alone cannot be relied upon to monitor a patient's response to hormone therapy; clinical criteria must also be considered.[71]

The serum behavior of testosterone and prostate-specific antigen in patients with prostate carcinoma between 2013 and 2015 in the province of Holguín revealed that the ratio of blood

testosterone and PSA values reflected those 101 patients with serum testosterone levels below 38 nmol/L and 3 had elevated levels. Among the patients studied, 89 had significantly elevated PSA blood levels, and 15 had values between 10 and 20 ng/ml, with a coefficient of variation of 2,9 for the serum testosterone level and 2,3 for the PSA level. The results of this research revealed that, after three years, testosterone increased, representing 86,4 % of the 19 patients, constituting a fundamental parameter for determining the moment of hormonal escape. The increase in the PSA level after one year constituted 52,6 % of the variation and was a sign of disease progression.[72,73]

Zoledronic acid is a third-generation bisphosphonate that is most commonly used for the treatment of bone metastases. It is approved for the prevention of bone complications in patients with advanced neoplasms affecting the bone.

Figure 2 shows that of the 36 patients with metastatic lesions who received zoledronic acid, 24 completed the treatment, whereas the results were inconclusive for 12 patients because of signs of renal failure with elevated creatinine levels secondary to nephrotoxicity. Follow-up scintigraphy revealed improvement in previous metastatic lesions in 20 patients but was unfavorable for 4 of them, where the lesions persisted.

Mundy et al. conducted a review of preclinical studies with bisphosphonates and reported a reduction in bone metastases. Green JR also conducted a preclinical review of the antitumor effects of bisphosphonates.[18] Based on these effects, a variety of potential mechanisms have been proposed: indirect effects on tumor cell growth in bone through the inhibition of bone resorption and osteoclastogenesis; induction of tumor cell apoptosis; inhibition of tumor cell adhesion to the extracellular matrix; reduction in metastatic potential; and inhibition of angiogenesis. Multiple in vitro studies have been conducted to demonstrate the antitumor activity of zoledronic acid. Corey et al. studied the effect of zoledronic acid on bone metastases in rats and reported that zoledronic acid did not affect prostate tumor growth but did inhibit the growth of osteoblastic and osteolytic metastases, exhibiting antitumor activity both in vitro and in vivo.[74]

CALGB-90202 was a randomized controlled trial comparing zoledronic acid (4 mg IV every 4 weeks) and placebo in 645 men with androgen deprivation-sensitive prostate cancer who had bone metastases. Patients with disease progression and resistance to hormone therapy received zoledronic acid without treatment masking.[48]

There was no difference between the two study groups in the primary endpoint of skeletal complications (defined as clinical fractures, spinal cord compression, episodes requiring palliative radiation or bone surgery, and death from prostate cancer) after a maximum follow-up of 7 years. [75, 76]

Androgen deprivation is associated with side effects such as obesity, erectile dysfunction, gynecomastia, insulin resistance, lipid metabolism disorders, loss of bone density, fatigue, and cognitive impairment, which impact patients' quality of life; it sometimes causes osteoporosis and bone fractures.

In a population sample of 50 613 Medicare patients aged 66 years or older who were followed for a median of 5,1 years, men treated with a gonadotropin-releasing hormone (GnRH) agonist or with orchiectomy had a bone fracture rate of 19,4 %, whereas this rate was 12,6 % for men

who did not receive hormone deprivation therapy. The effect was similar in men with or without metastatic bone disease. In randomized placebo-controlled trials, treatment of osteoporosis with bisphosphonates was found to reduce the risk of bone fractures in men.[77, 78]

This evaluation revealed that at the start of anti-androgen treatment, there was a drastic reduction in patients' erectile function and sexual desire, leading to erectile dysfunction in 48 % of patients. Gynecomastia and mastodynia accounted for 16 % and 14 %, respectively, of cases, followed by hot flashes or hot flushes, as they are often described, accounting for 10 %, and to a lesser extent, bone pain and hepatotoxicity.

Chapter 07 / Capítulo 07

Advanced Prostate Adenocarcinoma and Androgen Deprivation Therapy. Clinical Outcomes, Risk Stratification, and Therapeutic Results
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Operational recommendations and areas for improvement

A comprehensive review of the results presented throughout this book allows us to outline a map of clinical and organizational priorities for the management of advanced prostate adenocarcinoma under total androgen deprivation. The predominant profile of the cohort—older patients with a high-risk classification—is not an incidental detail: it guides the direction of each therapeutic decision and determines the type of follow-up that is reasonable, realistic, and ethically consistent. When the disease is diagnosed at an advanced stage, the horizon of clinical care shifts. The goals are no only expressed in terms of tumor control but also in terms of functional preservation, symptomatic relief, maintenance of autonomy, reduction in complications, and sustained support for the patient and their environment.

In this scenario, the operational question is not usually "what treatment is available," but "what treatment is appropriate here, for this patient, with this risk, with this history, with this family support, and with this health system." The decision requires weighing efficacy, tolerance, accessibility, continuity, and follow-up capacity. Total androgen deprivation occupies a central place because its impact on symptom control is tangible and because its biological rationale is consistent. Even so, hormone treatment is not a single act; it is a process. A process that needs clear rules, defined timelines, well-interpreted markers, and an honest clinical conversation about the expectations and human costs of treatment.

This chapter proposes operational recommendations and areas for improvement organized around five axes: (1) therapeutic selection and follow-up planning, (2) monitoring of progression and detection of hormone resistance, (3) adherence and therapeutic continuity, (4) comprehensive management of adverse effects with an emphasis on sexual function and quality of life, and (5) strengthening of clinical records and institutional coordination. The objective is not to establish a uniform prescription but rather to offer a replicable framework that allows for improved clinical consistency, reduced avoidable variability, and a more predictable institutional response to complex trajectories.

Therapeutic selection in advanced disease: practical criteria and clinical realism

When the diagnosis is established with advanced disease and high risk, therapeutic selection should avoid two extremes: inertia (maintaining the same regimen without periodic reevaluation) and impulsive change (modifying treatments without defined criteria). Total androgen deprivation, owing to its symptomatic control profile, can be sustained as a baseline treatment but requires an explicit follow-up plan. This plan should include what is monitored, how often, what thresholds trigger a reassessment, and what alternatives are considered if progression occurs.

Operational recommendations

- At the start of treatment, a written "follow-up itinerary" is defined in the medical records: frequency of consultations, tentative dates for biochemical measurements, symptom assessments, and monitoring of adverse events.
- Establish a scheduled (nonreactive) clinical reassessment point: a specific consultation to review biochemical response, functional status, symptoms, tolerance, and adherence.
- The objectives are differentiated on two levels: oncological objective (control of tumor activity and signs of progression) and well-being objective (symptoms, sleep,

energy, mood, sexuality, pain).

This approach prevents hormone therapy from becoming a repetitive practice. In older patients, therapeutic continuity is maintained when the patient understands the purpose of the treatment, recognizes what effects are to be expected, and perceives that there is a team attentive to their experience. Clinical trust is often a silent factor that sustains adherence, particularly when treatment changes intimate aspects of daily life.

Progression monitoring: integrated PSA, testosterone, and clinical readings

Progression in advanced prostate cancer does not always manifest in the same way. It can present as elevated markers, clinical changes, new images consistent with active disease, or a combination of these elements. This study revealed a guiding sequence: elevated PSA appears more frequently in the intermediate stages of follow-up, and elevated testosterone becomes more relevant in later stages, becoming a critical indicator in the recognition of hormonal escape. This observation can be translated into practical rules for monitoring.

The central recommendation is to abandon the isolated reading of markers. A rising PSA does not have the same meaning if testosterone is suppressed or if it has recovered to normal levels; similarly, rising testosterone raises questions about the actual effectiveness of the blockade, the regularity of treatment and factors that may explain loss of suppression.

Operational recommendations

- PSA and testosterone should be monitored in a coordinated manner, with a joint interpretation documented in the medical records.
- Define internal (operational) alert thresholds that require reassessment, even if behavior is not immediately modified. The value of a threshold lies not only in the number but also in the discipline of reviewing the patient when that limit is crossed.
- A structured clinical evaluation should be incorporated into each check-up to assess the following parameters: bone pain, urinary changes, weight loss, persistent fatigue, compressive symptoms, signs of obstruction, and recent functional alterations.

Areas for improvement

- A standard follow-up sheet that includes date, PSA, testosterone, main symptoms, and clinical decisions was designed. A simple tool reduces omissions and improves continuity between different professionals.
- Establish a pathway for “suspected hormone resistance”: biochemical confirmation, adherence review, androgen suppression verification, disease extension assessment, and therapeutic discussion.

This point is essential: hormonal escape should not be detected late. Early detection does not imply alarmism; it implies preparation. A system that anticipates scenarios reduces improvisation and better protects the patient.

Therapeutic adherence: understanding discontinuation as a clinical sign

During the observation period, adherence remained predominant, but there was a phase with an increase in nonadherence. In a book geared toward clinical practice, this finding should be read as a signal: adherence is not a fixed attribute of the patient; it is a relationship. When it fails, it rarely fails for a single reason.

Noncompliance can result from barriers to access, treatment fatigue, cumulative adverse effects, loss of confidence, denial, logistical difficulties, depressive symptoms, or lack of family support. If it is approached with a punitive approach ("the patient is not complying"), the likelihood of regaining continuity decreases. If it is approached as clinical data ("something is interfering"), the conversation changes.

Operational recommendations

- A brief adherence check at each consultation was performed, with simple, nonaccusatory questions concerning the following: actual frequency of administration, interruptions, difficulties, and adverse events that led to discontinuation.
- Document the probable cause of nonadherence when identified: adverse effects, access, forgetfulness, lack of understanding, personal conflicts, and emotional fragility.
- A standardized minimum intervention for nonadherence should be established: brief education, adjustment of adverse effect management, coordination with pharmacies/services, and early rescheduling of follow-up.

Areas for improvement

- Create an institutional support channel for therapeutic continuity: telephone coordination or brief consultation for patients who interrupt treatment or miss follow-up appointments.
- Identifying "critical points" of adherence, for example, periods when hot flashes, sexual dysfunction, fatigue, or mood swings tend to occur. If adverse effects are anticipated, the likelihood of silent abandonment is reduced.

In older patients, adherence is also supported by structure: reminders, family support, clear instructions, and closer follow-up when there are signs of frailty.

Adverse effects and daily life: placing sexual function at the center of care

This study revealed that erectile function was the main area affected after the start of hormone treatment. This finding deserves careful consideration, not as a side note but as a central part of medicine that recognizes the whole person.

Sexual dysfunction is not just an "expected" consequence of physiology; it can affect self-esteem, relationships, personal identity, intimacy, and emotional well-being. In cultural contexts where male sexuality is associated with ideas of vigor or social role, the impact can be even more profound. In the clinical setting, there is a risk of minimizing it out of modesty, lack of time, or the belief that "it does not matter in older patients." This risk impoverishes care and erodes trust.

Operational recommendations

- Explicitly open the conversation about sexuality before initiating androgen deprivation: Inform the patient about what to expect, ask about concerns, and record the patient's priorities.
- Sexual symptoms were assessed as part of follow-up, not just as an adverse event: desire, erection, satisfaction, physical discomfort, and changes in relationships.
- Offer alternative approaches as available: counseling, psychological support, education for the partner, pharmacological interventions when appropriate, and referral to sexology or functional urology if resources are available.

The goal is not always to "restore" function but rather to preserve dignity, reduce avoidable suffering, and sustain relationships. A well-conducted conversation does not create problems; it names what is already happening and allows the patient to feel supported.

Other reported adverse effects include vasomotor symptoms, gynecomastia, mastodynia, bone pain, and less frequent events with clinical relevance, such as hepatotoxicity. Each requires a specific response.

Operational recommendations

- Flashes/heat waves: The symptoms should be validated, their impact on sleep and quality of life should be quantified, and management measures should be proposed according to guidelines and resources.
- Gynecomastia and mastodynia: explain the mechanism, offer relief strategies, and assess the emotional impact.
- Bone pain: Bone pain can be differentiated into pain due to metastasis, bone fragility, or other causes, and evaluation can be coordinated with stepwise analgesia.
- Hepatotoxicity: Laboratory monitoring when justified by the pharmacological regimen and clear record of conduct in case of alteration.

Areas for improvement

- Incorporate a "minimum therapeutic education package" at the outset: a simple sheet with expected effects, warning signs, and contacts.
- Periodic quality-of-life assessment should be implemented with brief instruments, especially in patients with signs of depression, severe fatigue, or isolation.

Quality of life is not an abstract concept. It is measured in nights of sleep, in the ability to walk without pain, in the face of treatment, in the continuity of personal projects, and in sustained relationships.

Metastatic lesions and bone care: follow-up, prevention, and continuity

Bone metastases are among the most frequent manifestations of progression. Bone care is not an appendage to oncological management: it is a dimension of skeletal event prevention, pain control, mobility preservation, and autonomy protection.

The use of zoledronic acid and gamma ray monitoring, which has improved in some patients, suggests that the bone support strategy has an impact and should be more clearly integrated into the clinical pathway. The recommendation is to build a bone care pathway with three components: detection, intervention, and follow-up.

Operational recommendations

- To establish criteria for evaluating bone spread in patients with signs of progression, persistent pain, or significant biochemical elevation.
- Guidelines for monitoring pain and motor function should be defined as part of regular check-ups.
- The bone support treatment cycles were recorded, continuity was ensured, and the reasons for interruption (adverse effects, access, treatment fatigue) were identified.

Areas for improvement

- Coordination between urology, oncology, imaging, laboratory, and pain/palliative

care should be created when available, with clear referral pathways.

- Patient education on risk signs should be provided: new persistent pain, falls, sudden loss of strength, and neurological symptoms.

Preventing bone events not only reduces suffering but also reduces avoidable hospitalizations and protects clinical resources.

Clinical records and institutional intelligence: Standardizing to provide better care

One of the most impactful improvements is often the simplest: standardize record keeping. When follow-up depends on inconsistent notes, data are lost, decisions are repeated, detection of progression is delayed, and care is fragmented. This book already includes a data collection form/tool; that tool can evolve into a clinical care format.

Operational recommendations

- A standard control sheet for each consultation was designed: PSA, testosterone, key symptoms, adverse effects, adherence, clinical decisions, and planning for the next evaluation.
- Minimum mandatory fields should be incorporated: risk classification, stage, hormone regimen, start date, and reason for changes.
- Explicitly recording the interpretation of markers is not enough to note values; it must be clear what they mean for the team.

Areas for improvement

- An institutional basis for advanced cases should be established, with periodic review of indicators such as percentage with bone progression, frequency of hormone resistance, therapeutic continuity, and major adverse events.
- Brief clinical audits of patients with rapid progression or therapeutic interruption should be performed with a formative, not punitive, approach.

Institutional intelligence does not replace clinical intelligence; it supports it. A team that learns from its own data has an improved ability to anticipate and reduce avoidable variability.

Interpretative limitations and scope of applied research

The study is based on a descriptive cross-sectional observational design in a specific healthcare setting. This framework adds value owing to its proximity to real practice, but it also limits the type of statements that can be made. The interpretation does not attempt to establish causality or automatically generalize to other contexts. The value lies in describing trajectories and patterns that, within this institutional setting, guide clinical decisions and raise questions.

In terms of future development, there are lines of applied research that can strengthen the understanding of the phenomenon and improve care: longitudinal studies with longer follow-up, incorporation of standardized quality of life instruments, analysis of factors associated with nonadherence, and comparative evaluation of therapeutic regimens according to risk and comorbidity profiles. It is also important to delve deeper into qualitative dimensions: how patients experience hormone treatment, what barriers they perceive, what expectations they have, and what fears condition their therapeutic continuity.

Closing the chapter: more predictable, humane, and consistent clinical practice

The recommendations made in this chapter are based on a simple idea: advanced disease requires care that is not improvised. Total androgen deprivation allows symptomatic control and provides a solid therapeutic framework, but its clinical effectiveness depends on integrated monitoring, therapeutic continuity, real attention to adverse effects, and an institutional culture that records, reviews, and acts.

The predominance of older, high-risk patients reminds us that care must be proportional to the frailty and human impact of treatment. Detecting hormone resistance requires clinical discipline: PSA and testosterone are read together, with thresholds for reassessment and clear response pathways. Adherence should be treated as clinical data that invites understanding, not as a judgment. The sexual sphere should no longer be a taboo topic: its impact affects quality of life and psychological well-being.

If the system manages to integrate these elements—planned follow-up, coordinated reading of markers, structured management of adverse effects, bone care, and standardized recording—treatment ceases to be a set of isolated acts and becomes a coherent clinical process. This process not only improves care but also builds trust and dignity in scenarios where uncertainty often accompanies the patient from diagnosis onward.

REFERENCES

1. Achard V, Putora PM, Omlin A, Zilli T, Fischer S. Metastatic prostate cancer: treatment options. Oncology (Switzerland). 2022;100:48-59. doi:10.1159/000519861.

2. Adami H-O, Bergström R, Engholm G, Nyren O, Wolk A, Ekbom A, et al. A prospective study of smoking and risk of prostate cancer. Int J Cancer. 1996;67(6):764-768.

3. Zafeiriou Z, Bianchini D, Chandler R, Rescigno P, Yuan W, Carreira S, et al. Genomic analysis of three metastatic prostate cancer patients with exceptional responses to carboplatin indicating different types of DNA repair deficiency. Eur Urol. 2019;75:184-192. doi:10.1016/j.eururo.2018.09.048.

4. Antonarakis ES, Gomella LG, Petrylak DP. When and how to use PARP inhibitors in prostate cancer: a systematic review of the literature with an update on on-going trials. Eur Urol Oncol. 2020;3:594-611. doi:10.1016/j.euo.2020.07.005.

5. Antonarakis ES, Isaacsson-Velho P, Fu W, Wang H, Agarwal N, Santos VS, et al. CDK12-altered prostate cancer: clinical features and therapeutic outcomes to standard systemic therapies, poly (ADP-ribose) polymerase inhibitors, and PD-1 inhibitors. 2019;3:370-381. doi:10.1200/PO.19.00399.

6. Sociedad Argentina de Urología. Consenso Nacional Inter-Sociedades para el Diagnóstico y Tratamiento de las Neoplasias Renales Parenquimatosas del Adulto. 2015. http://www.socargcancer.org.ar/consensos/2015_inter_soc_neoplasias_renales.pdf

7. Eble JN, World Health Organization, International Agency for Research on Cancer, International Academy of Pathology. Pathology and genetics of tumours of the urinary system and male genital organs. Lyon; Oxford: IARC Press; Oxford University Press (distributor); 2004. http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&db=nlabk&AN=174876

8. Attard G, Murphy L, Clarke NW, Sachdeva A, Jones C, Hoyle A, et al. Abiraterone acetate plus prednisolone with or without enzalutamide for patients with metastatic prostate cancer starting androgen deprivation therapy: final results from two randomised phase 3 trials of the STAMPEDE platform protocol. Lancet Oncol. 2023;24:443-456. doi:10.1016/S1470-2045(23)00148-1.

9. Ministerio de Salud Pública. Anuario Estadístico de Salud. La Habana: Ministerio de Salud Pública; 2017. https://temas.sld.cu/estadisticassalud/2020/05/13/publicado-el-anuario-estadistico-de-salud-2019/

10. Ministerio de Salud Pública. Registro Nacional del Cáncer. 2020. https://instituciones.sld.cu/sicc/registro-nacional-del-cancer/

11. Auchus RJ, Sharifi N. Sex hormones and prostate cancer. Annu Rev Med. 2020;71:33-45. doi:10.1146/annurev-med-051418-060357.

12. Bansal D, Reimers MA, Knoche EM, Pachynski RK. Immunotherapy and immunotherapy combinations in metastatic castration-resistant prostate cancer. Cancers. 2021;13:1-22. doi:10.3390/cancers13020334.

13. Banski MA, Chagas MA, Pereira MJ. Morfología y fracción del área del lumen glandular de la zona de transición en la próstata humana. Rev Chil Anat. 2002;:255-262.

14. Bland CS. The Halsted mastectomy: present illness and past history. West J Med. 1981;134(6):549-555.

15. Breathnach CS. Rudolf Virchow (1821-1902) and Die Cellularpathologie (1858). J Ir Coll Physicians Surg. 2002;31(1):43-46.

16. Carvalho P de. Urologia: texto basico para estudantes de medicina. Rio de Janeiro: Atheneu; 1988.

17. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med. 2005;352(2):154-164. doi:10.1056/NEJMoa041943. PMID: 15647578. https://pubmed.ncbi.nlm.nih.gov/15647578/

18. Chan JM, Giovannucci E, Andersson S-O, Yuen J, Adami H-O, Wolk A. Dairy products, calcium, phosphorous, vitamin D, and risk of prostate cancer (Sweden). Cancer Causes Control. 1998;9(6):559-566.

19. Chapple CR, Steers WD, Evans CP. Urologic principles and practice. 2020.

20. Chowdhury S, Bjartell A, Lumen N, Maroto P, Paiss T, Gõmez-Veiga F, et al. Real-world outcomes in first-line treatment of metastatic castration-resistant prostate cancer: the Prostate Cancer Registry. Target Oncol. 2020;15:301-315. doi:10.1007/s11523-020-00720-2.

21. Gillessen S, Attard G, Beer TM, Beltran H, Bjartell A, Bossi A, et al. Management of patients with advanced prostate cancer: report of the Advanced Prostate Cancer Consensus Conference 2019. 2020;77:508-547. doi:10.1016/j.eururo.2020.01.012.

22. Gillessen S, Bossi A, Davis ID, De Bono J, Fizazi K, James ND, et al. Management of patients with advanced prostate cancer. Part I: intermediate-/high-risk and locally advanced disease, biochemical relapse, and side effects of hormonal treatment: report of the Advanced Prostate Cancer Consensus Conference 2022. 2023;83:267-293. doi:10.1016/j.eururo.2022.11.002.

23. Gillessen S, Bossi A, Davis ID, De Bono J, Fizazi K, James ND, et al. Management of patients with advanced prostate cancer—metastatic and/or castration-resistant prostate cancer: report of the Advanced Prostate Cancer Consensus Conference (APCCC) 2022. 2023;185:178-215. doi:10.1016/j.ejca.2023.02.018.

24. Catalona WJ, Southwick PC, Slawin KM, Partin AW, Brawer MK, Flanigan RC, et al. Comparison of percent free PSA, PSA density, and age-specific PSA cutoffs for prostate cancer detection and staging. Urology. 2000;56(2):255-260.

25. Xiang Z, Xu C, Wu G, Liu B, Wu D. CircRNA-UCK2 increased TET1 inhibits proliferation and invasion of prostate cancer cells via sponge miRNA-767-5p. Open Med (Wars). 2020;14:833-842. doi:10.1515/med-2019-0097.

26. Corey E, Brown LG, Quinn JE, Poot M, Roudier MP, Higano CS, Vessella RL. Zoledronic acid exhibits inhibitory effects on osteoblastic and osteolytic metastases of prostate cancer. Clin Cancer Res. 2003;9(1):295-306. Erratum in: Clin Cancer Res. 2003;9(4):1574-1575. PMID: 12538482. https://pubmed.ncbi.nlm.nih.gov/12538482/

27. Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De-

Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II—2020 update: treatment of relapsing and metastatic prostate cancer. Eur Urol. 2021;79:263-282. doi:10.1016/j.eururo.2020.09.046.

28. Dai C, Dehm SM, Sharifi N. Targeting the androgen signaling axis in prostate cancer. J Clin Oncol. 2023;41:4267-4278. doi:10.1200/JCO.23.00433.

29. DeAntoni EP, David Crawford E, Oesterling JE, Ross CA, Roy Berger E, McLeod DG, et al. Age- and race-specific reference ranges for prostate-specific antigen from a large community-based study. Urology. 1996;48(2):234-239.

30. Deegen P, Thomas O, Nolan-Stevaux O, Li S, Wahl J, Bogner P, et al. The PSMA-targeting half-life extended BiTE therapy AMG 160 has potent antitumor activity in preclinical models of metastatic castration-resistant prostate cancer. Clin Cancer Res. 2021;27:2928-2937. doi:10.1158/1078-0432.CCR-20-3725.

31. Koochekpour S, Hu SY, Subramani D, Majumdar S, Liu Z, Velasco-GonzaleZ Cruz, et al. 142 somatic and genomic instability of androgen receptor in african americans with prostate cancer. J Urol. 2011;185(4 Suppl):e60-e60.

32. Desai K, McManus JM, Sharifi N. Hormonal therapy for prostate cancer. Endocr Rev. 2021;42:354-373. doi:10.1210/endrev/bnab002.

33. Dong L, Zieren RC, Xue W, de Reijke TM, Pienta KJ. Metastatic prostate cancer remains incurable, why? Asian J Urol. 2019;6:26-41. doi:10.1016/j.ajur.2018.11.005.

34. Drake RL, Vogl W, Mitchell AWM, Tibbitts R, Richardson PE, Gray H. Gray's atlas of anatomy. 2015.

35. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. A prospective cohort study of vasectomy and prostate cancer in US men. JAMA. 1993;269(7):873-877.

36. Espana F, Royo M, Martinez M, Enguidanos MJ, Vera CD, Estelles A, et al. Free and complexed prostate specific antigen in the differentiation of benign prostatic hyperplasia and prostate cancer: studies in serum and plasma samples. J Urol. 1998;160(6 Pt 1):2081-2088.

37. Espuela R, Nogueras MA, Abad F, Passas J. Ecografía transrectal de próstata: técnica e indicaciones. Actas Urol Esp. 1985;9:317.

38. Farber S, Diamond LK, Mercer RD, Sylvester RF, Wolff JA. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). N Engl J Med. 1948;238(23):787-793.

39. Witte JS. Prostate cancer genomics: towards a new understanding. Nat Rev Genet. 2009;10(2):77-82.

40. Zhao SG, Chen WS, Li H, Foye A, Zhang M, Sjöström M, et al. The DNA methylation landscape of advanced prostate cancer. Nat Genet. 2020;52:778-789. doi:10.1038/s41588-020-0648-8.

41. Feng Q, He B. Androgen receptor signaling in the development of castration-resistant

prostate cancer. Front Oncol. 2019;9. doi:10.3389/fonc.2019.00858.

42. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. Int J Cancer. 2012;136:E359-E386.

43. Fernández L, Galán Y, Jiménez R, Gutiérrez Á, Guerra M, Pereda CM, et al. Estudio de casos y controles sobre factores de riesgo de cáncer de próstata. Rev Cubana Salud Publica. 2005;31(3). http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S0864-34662005000300002&lng=es

44. Ferrer Casero E. Morfofisiología del sistema urinario. En: Urología. La Habana: ECIMED; 2012.

45. Fleshner N, Trachtenberg J. New developments and controversies in androgen derivation therapy for advanced prostatic carcinoma. AUA Update Series Lesson. 1997;12.

46. Formaggio N, Rubin MA, Theurillat J-P. Loss and revival of androgen receptor signaling in advanced prostate cancer. Oncogene. 2021;40:1205-1216. doi:10.1038/s41388-020-01598-0.

47. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst. 1996;88(16):1118-1126.

48. Smith MR, Halabi S, Ryan CJ, Hussain A, Vogelzang N, Stadler W, et al. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (Alliance). J Clin Oncol. 2014;32(11):1143-1150. doi:10.1200/JCO.2013.51.6500. PMID: 24590644. PMCID: PMC3970172. https://pubmed.ncbi.nlm.nih.gov/24590644/

49. Gohji K, Morisue K, Kizaki T, Fujii A. Correlation of transrectal ultrasound imaging and the results of systematic biopsy with pathological examination of radical prostatectomy specimens. Br J Urol. 1995;75(6):758-765.

50. Grisanzio C, Freedman ML. Chromosome 8q24-associated cancers and MYC. Genes Cancer. 2010;1(6):555-559.

51. Zhang Z, Karthaus WR, Lee YS, Gao VR, Wu C, Russo JW, et al. Tumor microenvironment-derived NRG1 promotes antiandrogen resistance in prostate cancer. Cancer Cell. 2020;38:279-296.e9. doi:10.1016/j.ccell.2020.06.005.

52. Guadalajara VJV, Cayuelas LM, Sanz PS, Caballero LS, Hernández RP, Sempere FSC, et al. Terapia de deprivación androgénica en cáncer de próstata avanzado. Estudio multicéntrico. Arch Esp Urol. 2020;73(6):499-508.

53. Hamid AA, Huang H-C, Wang V, Chen Y-H, Feng FY, Den R, et al. Transcriptional profiling of primary prostate tumor in metastatic hormone-sensitive prostate cancer and association with clinical outcomes: correlative analysis of the E3805 CHAARTED trial. Ann Oncol. 2021;32:1157-1166. doi:10.1016/j.annonc.2021.06.003.

54. Hansen JT, Netter FH. Netter. Anatomía clínica. 2015.

55. Hearn JWD, Sweeney CJ, Almassi N, Reichard CA, Reddy CA, Li H, et al. HSD3B1 genotype

and clinical outcomes in metastatic castration-sensitive prostate cancer. JAMA Oncol. 2020;6. doi:10.1001/jamaoncol.2019.6496.

56. Heidenreich A, Bolla M, Joniau S, Mason MD, Matveev V, Mottet N, et al. Guía clínica sobre el cáncer de próstata. Asociación Europea de Urología; 2010. http://fau.org.ar/docs/GUIA-CLINICA-SOBRE-EL-CANCER-DE-PROSTATA_espanol.pdf

57. Herranz Amo F. Atlas de ecografía transrectal de próstata. Barcelona: Doyma; 1999.

58. Hollander MC, Blumenthal GM, Dennis PA. PTEN loss in the continuum of common cancers, rare syndromes and mouse models. Nat Rev Cancer. 2011;11(4):289-301.

59. Hoyos Gorrotxategi L. Resiliencia: una propuesta enfermera en la supervivencia del cáncer. Tesis de grado. Navarra: Universidad Pública de Navarra; 2021. https://academica-e.unavarra.es/bitstream/handle/2454/39824/Hoyos%20Gorrotxategi%2C%20Lara.pdf?sequence=1&isAllowed=y

60. Hsu E-C, Rice MA, Bermudez A, Marques FJG, Aslan M, Liu S, et al. Trop2 is a driver of metastatic prostate cancer with neuroendocrine phenotype via PARP1. Proc Natl Acad Sci U S A. 2020;117:2032-2042. doi:10.1073/pnas.1905384117.

61. Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med. 2013;368(14):1314-1325.

62. Isaacsson-Velho P, Fu W, Wang H, Mirkheshti N, Qazi F, Lima FAS, et al. Wnt-pathway activating mutations are associated with resistance to first-line abiraterone and enzalutamide in castration-resistant prostate cancer. Eur Urol. 2020;77:14-21. doi:10.1016/j.eururo.2019.05.032.

63. James ND, Clarke NW, Cook A, Ali A, Hoyle A, Attard G, et al. Abiraterone acetate plus prednisolone for metastatic patients starting hormone therapy: 5-year follow-up results from the STAMPEDE randomised trial (NCT00268476). Int J Cancer. 2022;151:422-434. doi:10.1002/ijc.34018.

64. Jung K, Stephan C, Elgeti U, Lein M, Brux B, Kristiansen G, et al. Molecular forms of prostate-specific antigen in serum with concentrations of total prostate-specific antigen <4 µg/L: are they useful tools for early detection and screening of prostate cancer? Int J Cancer. 2001;93(5):759-765.

65. Nimir M, Ma Y, Jeffreys SA, Opperman T, Young F, Khan T, et al. Detection of AR-v7 in liquid biopsies of castrate resistant prostate cancer patients: a comparison of AR-v7 analysis in circulating tumor cells, circulating tumor RNA and exosomes. Cells. 2019;8. doi:10.3390/cells8070688.

66. Kim NH, Kim S-N, Kim YK. Involvement of HDAC1 in E-cadherin expression in prostate cancer cells; its implication for cell motility and invasion. Biochem Biophys Res Commun. 2011;404(4):915-921.

67. Kohli M, Tan W, Zheng T, Wang A, Montesinos C, Wong C, et al. Clinical and genomic insights into circulating tumor DNA-based alterations across the spectrum of metastatic hormone-sensitive and castrate-resistant prostate cancer. EBioMedicine. 2020;54. doi:10.1016/j.ebiom.2020.102728.

68. Koochekpour S. Androgen receptor signaling and mutations in prostate cancer. Asian J Androl. 2010;12(5):639-657.

69. Mohler JL, Antonarakis ES. NCCN guidelines updates: management of prostate cancer. J Natl Compr Canc Netw. 2019;17:583-586. doi:10.6004/jnccn.2019.5011.

70. Schaeffer EM, Srinivas S, Adra N, An Y, Barocas D, Bitting R, et al. NCCN Guidelines® Insights: prostate cancer, version 1.2023: featured updates to the NCCN guidelines. J Natl Compr Canc Netw. 2022;20:1288-1298. doi:10.6004/jnccn.2022.0063.

71. Kułakowski A. The contribution of Marie Skłodowska-Curie to the development of modern oncology. Anal Bioanal Chem. 2011;400(6):1583-1586.

72. Kumar RJ, Barqawi A, Crawford ED. Adverse events associated with hormonal therapy for prostate cancer. Rev Urol. 2005;7(Suppl 5):S37-S43.

73. Mason MD, Sydes MR, Glaholm J, Langley RE, Huddart RA, Sokal M, et al; Medical Research Council PR04 Collaborators. Oral sodium clodronate for nonmetastatic prostate cancer—results of a randomized double-blind placebo-controlled trial: Medical Research Council PR04 (ISRCTN61384873). J Natl Cancer Inst. 2007;99(10):765-776. doi:10.1093/jnci/djk178. PMID: 17505072. https://pubmed.ncbi.nlm.nih.gov/17505072/

74. McAninch JW, Lue TF, Pineda Rojas E. Smith y Tanagho: urología general. 18a ed. McGraw-Hill Interamericana; 2000.

75. McAninch JW, Smith DR, Tanagho EA. Smith & Tanagho's general urology. New York: McGraw-Hill; 2013.

76. Parsons JK, Brawer MK, Cheli CD, Partin AW, Djavan R. Complexed prostate specific antigen (PSA) reduces unnecessary prostate biopsies in the 2.6-4.0 ng/mL range of total PSA. BJU Int. 2004;94(1):47-50.

77. Patel GK, Chugh N, Tripathi M. Neuroendocrine differentiation of prostate cancer—an intriguing example of tumor evolution at play. Cancers. 2019;11. doi:10.3390/cancers11101405.

78. Perdana NR, Mochtar CA, Umbas R, Hamid ARA. The risk factors of prostate cancer and its prevention: a literature review. Acta Med Indones. 2017;48(3):228-238.