

Chapter 02 / Capítulo 02

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

ISBN: 978-9915-9869-7-5

DOI: 10.62486/978-9915-9869-7-5.Ch02

Pages: 6-23

©2024 The authors. This is an open access book distributed under the terms of the Creative Commons Attribution (CC BY) 4.0 License.

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 [HPC1]), 1q23-25), ELAC2 (HPC2 region, 17p), and MSRL (8p22-23). Segregation studies also suggest the existence of susceptibility sites or loci on chromosome 1q42.2-43 (PCAP).

Among the known susceptibility genes, HPC1 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)-I is a peptide hormone that promotes growth in adolescence and childhood and is associated with lean body mass in adults. IGF-I promotes cell proliferation and inhibits apoptosis in normal cells and prostate tumor cells. IGF-I 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 DU145 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 10q23, 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 $\geq$ 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 $\leq 50\%$ 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⁾