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.