Prostate cancer

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Abstract

Prostate cancer is the most frequent tumor found in men worldwide and in Mexico in particular. Age and family history are the main risk factors. The diagnosis is made by prostate biopsy in patients with abnormalities detected in their prostate-specific antigen (PSA) levels or digital rectal exam (DRE). This article reviews screening and diagnostic methods as well as treatment options for patients diagnosed with prostate cancer.

Keywords: prostate cancer; risk factors; diagnosis; treatment; prevention

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Resumen

El cáncer de próstata es el tumor más frecuente en hombres a nivel mundial, y de manera específica en México. Los principales factores de riesgo son la edad y la historia familiar. El diagnóstico se obtiene por medio de biopsia prostática en pacientes detectados por anormalidades en el antígeno prostático o tacto rectal. En este artículo se hace una discusión de los métodos de tamizaje, diagnóstico y opciones de tratamiento en pacientes con diagnóstico de cáncer de próstata.

Palabras clave: cáncer de próstata; factores de riesgo; diagnóstico; tratamiento; prevención

Prostate cancer (PC) is the most common cancer and the leading cause of cancer death in men over 50 y in Mexico. In 2015, 41 210 cancer deaths are expected among men, 6 801 of which will be from PC.[1] Prostate-specific antigen (PSA) has been applied as a useful marker for the early diagnosis and monitoring of PC. A randomized study in Europe demonstrated a progressive decrease in prostate cancer mortality, with a 51% reduction in individuals up to 75 years old who underwent screening.[2] As there is no malignant tumor follow-up registry in Mexico, PC prevalence and the consequent impact of PSA screening cannot be accurately measured. Multiple fundamental prognostic factors for PC (among others[3,4]) have been considered: 1. PSA determination: men under 40 years with PSA > 1 ng/mL present a higher PC risk and should be periodically monitored. 2. Disease stage at diagnosis: 70-80% of cases are restricted to the prostate. 3. The Gleason grading system (PC differentiation grade assessed by prostate biopsy): 75-80% of tumors are moderately differentiated (Gleason 7).

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Risk factors

Age and heredity, particularly grandparents, parents, siblings or other close relatives with a history of breast, ovarian or cervical tumors, are the only two risk factors clearly associated with PC development. 1. Age. Some 36.3% of cases are diagnosed during the seventh decade, with 31.6% between 70 and 79 years. 2. Heredity. PC may be hereditary in 10% of cases, with approximately 2- to 3-fold increased risk, which increases to up to 5-fold greater risk if more than one relative is affected. Moreover, several genes have been recognized to be involved in PC development, which makes it a polygenic disease. Studies have revealed the utility of measuring polymorphisms in genes such as *ELAC2* (with a role in tubulin function), *RNASEL* (an endoribonuclease that acts as a tumor suppressor gene) and *MSR1* (mutations in this gene confer a predisposition to chronic inflammatory conditions) to predict tumor behavior and aggressiveness. 3. Race. In the United States of America (USA), there are 250 000 new PC cases and 27 000 deaths every year. Over 50% of these deaths occur among African-Americans, followed by whites, Hispanic-Americans and less commonly among Asians. The possibility of developing PC is 17%, and death from the same cause is 3%. 4. Inflammation. Inflammation has been proposed as a risk factor for PC, particularly chronic inflammatory processes affecting the prostate. However, this is a controversial argument, and no causality has been confirmed. 5. Hormones. The participation of androgens and estrogens in the origin of PC is well known. Patients with congenital androgen deficiencies rarely develop PC or prostatic hyperplasia (PH). However, if androgen ablation is performed after puberty, these patients may develop PC or PH.[5,6] 6. Metabolic syndrome. The presence of two or more components of metabolic syndrome has been associated with a higher risk of PC, recurrence and/or progression.[7] 7. There are numerous studies on the protective roles of vitamins E and D, selenium, calcium and omega 3 and 6 fatty acids in the prevention of PC. However, no definitive cause-effect relationship has been found. Individuals who consume a Mediterranean diet high in antioxidants present a lower PC frequency.[8-11] Asian populations that have migrated to the USA present a higher incidence of PC compared with those who remain in their country of origin. This is possibly due to the adoption of new eating habits unlike those in their country of origin. This pattern supports the idea that certain nutritional factors may modify PC rates. 8. Smoking. Smoking has been associated with increased PC risk because the increased levels of circulating cadmium increase cellular oxidation. However, no causality has been established between these two conditions. 9. Exercise. Exercise is considered a protective factor, mainly for quality of life with or without PC, and thus is highly recommended.[12-14]

Diagnosis

In the current PSA era, a PC diagnosis is made 5 to 10 years before symptoms appear. In general, patients are asymptomatic or show symptoms of urinary voiding and/or storage related to PC. These involve decreased urinary stream, pushing, frequency, urgency and vesical tenesmus. Advanced PC symptoms include bone pain, renal failure, hematuria, pathological bone fractures, physical exhaustion and weight loss. The most significant tools for PC diagnosis are PSA levels (>4 ng/ml) and a suspicious digital rectal examination (DRE) (e.g., increased consistency or nodules). However, other factors can also increase PSA levels in the absence of PC: ejaculation, trauma (e.g., rectal, transurethral catheter placement), inflammation and infection (acute prostatitis), as well as prostatic hyperplasia. There can be significant inter-individual variation; thus, at least two measurements taken at least 3 weeks apart are required. One of the limitations of PSA screening is that its high sensitivity and low specificity lead to false positives. In some countries, the reference value is set at 2.5 ng/ml, which has resulted in many unnecessary prostate biopsies (BxP) (80% of cases) and overtreatment. It is also worth mentioning that up to 5% of PCs do not show increased PSA levels, so DRE may be the only effective diagnostic tool. Up to 18% of PC cases are diagnosed by DRE. Other PSA-derived measurements have also been described, such as PSA density, transition zone PSA density and other molecular methods. However, these PSA-derived measurements present limited practical utility. Free PSA (<25%) is another useful measurement when the PSA level ranges between 4 and 10 ng/ml, particularly in patients who already have a negative BxP. In theory, a fraction of this antigen can be produced by hyperplastic cells, not by malignant cells. In another test, the PCA3 marker from the non-coding prostate-specific mRNA is measured in urine sediment that is obtained after prostatic massage. The main advantages of this method over PSA are its higher sensitivity and specificity and the fact that it is not related to prostate volume or to prostatitis. However, its clinical utility is limited, and its use is mainly indicated for patients with a negative BxP and a progressive increase in PSA.

Screening

The diagnosis of locally advanced or metastatic PC decreased by as much as 75% between 1993 and 2003.

In 2009, the American group PLCO (Prostate, Lung, Colorectal and Ovarian Screening Trial) and the European group ERSPC (European Randomized Study on Screening for Prostate Cancer) separately published the results of two multicenter studies that assessed PSA screening as a diagnostic tool.[15] The results were contradictory. The PLCO group concluded that there was no difference in the reduction of PC-related mortality between the control and screened groups after 11 years of follow-up.[16,17] By contrast, the ERSPC group showed a 20% decrease in the PC-related mortality of 1000 patients after 9 years of follow-up.[18,19] Screening requires a proper medical and hospital infrastructure to assist all PC-diagnosed cases, which is not the case for Mexico. Indications for carrying out the PSA test must be discussed with the patient (e.g., advantages, complications and cost-benefit ratio). The current problem is that we do not have a marker or an imaging test that allows us to determine which cases of PC are aggressive vs indolent and should be monitored. We suggest PSA testing in patients older than 40-45 years, with the frequency of subsequent monitoring increased for values > 1 ng/ml (>40 years), given that the possibility of PC development is higher in such cases.[4] It should also be noted that life expectancy with PC is more than 10 years, as PC mortality is generally low (3%), and that the patients' comorbidities may have higher mortality (e.g., cardiovascular disease).

Prostate biopsy

Prostate biopsy (BxP) is the current standard for the diagnosis of PC. There are two main criteria for a patient to be considered a candidate for a BxP: a suspicious DRE and a PSA result higher than 4 ng/ml, obtained under ideal conditions and confirmed with two separate measurements at least 3 weeks apart. It is important to take into consideration the size of the prostate as measured by DRE or ultrasound. For example, if the prostate is small and the PSA is high, the possibility of PC is higher. If the prostate is larger (> 40 grams) and PSA values are between 4 and 10 ng/ml, the PH likelihood is 80%. The patient must be informed of all steps of the procedure, the diagnostic and therapeutic implications and the risks that these entail. It is imperative to treat the patient with a broad-spectrum antibiotic prior to the procedure. The most commonly used antibiotics are quinolones. However, in our own center in the National Institute of Medical Sciences and Nutrition, this group of antibiotics shows a higher resistance rate. We therefore use Piperacillin/Tazobactam with good results.[20] The BxP is performed by transrectal ultrasound and under sedation. At the beginning, a conventional ultrasound should be performed to visualize the prostate gland, the seminal vesicles and the bladder surface. The volume of the prostate gland is then calculated, and sextant biopsies are performed. Samples are obtained by puncturing the entire gland surface, attempting to obtain samples from the peripheral zone (75% of adenocarcinomas depend on this area). A total of 12 fragments are conventionally obtained, six from each lobe.[21] The risks associated with this procedure are mainly bleeding (rectal bleeding, hematospermia and hematuria) and fever (urinary tract infections, sepsis). These symptoms present in approximately 2 to 20% of all procedures worldwide. In our institution, these complications do not exceed 4.6%.[22] The objective of the biopsy is to obtain representative samples of the entire prostate gland for the pathologist to establish an accurate histological diagnosis. Biopsies are defined by their corresponding zone, so that the pathologist can determine the extent and laterality of the tumor. The most common prostate tumor is adenocarcinoma. The Gleason scale of histological differentiation is used for classification. This scale is fundamental for defining the stage and prognosis of PC patients. The scale is applied additively, with the first number representing the predominant histologic grade and the second number the secondary histologic grade. According to this reasoning, a Gleason value of 7 can reflect a 3+4 tumor (where 3 is the first number, i.e., less aggressive) or a 4+3 tumor (where 4 is the first number, i.e., more aggressive).

Staging

The stage of the disease plays a decisive role for both prognostic and therapeutic purposes. In general, we use the TNM scale to classify clinical and pathological stages. There are also other validated scales to group patients according to their risk of recurrence and mortality, of which the most often used is the D'Amico scale.[23] This scale evaluates PSA levels, the Gleason biopsy scale and the DRE, dividing patients into low risk (Gleason £ 6, PSA < 10 ng/mL and a stage of T1-T2a); intermediate risk (Gleason 7, PSA 10-20 ng/mL and T2b stage); and high risk (Gleason 8-10, PSA > 20 ng/ml and a stage greater than T2c). The importance of this classification lies in the differing 10-year survival rates for each group: 83% for the low-risk group, 46% for the intermediate-risk group and 29% for the high-risk group. However, numerous imaging techniques have also been used to evaluate extraprostatic extension and extension to lymph nodes (locally advanced disease) and to other structures, such as bone (metastatic disease). Some of these techniques include computed tomography of the chest, abdomen and pelvis, as well as MRIs and bone

scans. These techniques are recommended for patients in the intermediate- and high-risk groups. Evaluation of alkaline phosphatase levels, which are associated with bone metastasis, is also recommended.

Treatment

Prostate cancer is a slowly developing disease, and according to the age at diagnosis, patients may die from other causes, such as diabetes, cardiovascular diseases and stroke, among others. Therefore, an individualized assessment is required to determine which therapeutic modalities are the most suitable in each case.

Treatment for localized disease

a. Active monitoring

There is broad evidence that cases with low-risk PC and some with intermediate-risk PC with low tumor volume can be monitored. The goal is to detect the 30% of tumors that are most aggressive and require other treatment modalities, such as radical prostatectomy and radiation. In some very special cases, high-intensity focused ultrasound (HIFU) or cryotherapy is also required. The cancer-specific mortality is minimal (approximately 3%) at 10 and 15 years in patients with a 3+3 Gleason grade. Active monitoring is performed with PSA and annual biopsies to determine disease progression; if progression occurs, decisions are made together with the patient concerning the use of other treatment modalities.[24-26] Statistical models have been developed to predict the progression of a tumor. The Epstein criteria stand out among them and are the origin of the term "insignificant cancer" (tumor volume less than 0.2 cc, Gleason < 7 and organ-confined disease). To date, no tumor marker can classify PC as indolent or insignificant. Passive monitoring is an option for patients at low risk and with other comorbidities that do not allow them greater than 10-year survival.[25] In this case, a common strategy is to treat symptoms once they appear (e.g., if urinary retention exists, transurethral prostatic resection is applied; if there are pathological fractures, treatment is applied according to the fracture site). The patients who likely benefit most from monitoring are those with low-risk or indolent tumors and those who present other comorbidities with a lower than 10-year survival.

b. Radical prostatectomy

Radical prostatectomy (RP) as a treatment for PC has existed for over 100 years. Controversies have arisen regarding this procedure due to the two studies that assessed the survival of a group with RP versus a group with monitoring only. The European study found lower PC mortality in the RP group than the observation group (14.6 vs 20.7%, respectively) and a lower rate of metastasis development after 15 years (21.7% in the RP group vs 33.4% in the observation group). The USA study did not find differences between the two groups.[25-27] The most common complications related to RP are urinary incontinence (5-20%) and injury to the neurovascular bundles that regulate erection, which results in erectile dysfunction (ED) (40 and 80%).[28-31] The significant impacts of these two complications explain why other more conservative treatments are receiving growing acceptance. The National Comprehensive Cancer Network (NCCN) recommends a geriatric assessment in all patients over 65 with oncological disease to choose the therapy with the least physical impact and thus better quality of life for the patient.[32] The last 10 years have seen an increase in the use of new technologies for the surgical treatment of PC, such as laparoscopic and robotic techniques. Although these techniques have not shown improvements in cancer control, urinary incontinence or erectile dysfunction compared to open surgery, they show better results regarding bleeding, hospital stays and cosmetic appearances. Therefore, treatment options should be explained in detail, and the patient should decide which option fits best.

c. Radiotherapy

3D-conformal radiotherapy (RT) has shown comparable results to RP in the oncological control of PC without the immediate surgical morbidities. However, it is associated with other previously acknowledged morbidities in the medium and long term, such as ED and urinary incontinence. Studies have shown that among patients treated with RT, those under 72 have an increased overall survival compared with those over 72, regardless of comorbidities.[32,33]

d. Other modalities

Cryotherapy, brachytherapy and high intensity focused ultrasound (HIFU) have also been proposed as treatment options for localized disease. The goal of these methods is to achieve tissue necrosis either from seeds of radioactive material (brachytherapy), freezing (cryotherapy) or ultrasonic waves (HIFU). Control rates have improved to levels comparable to those achieved with radiotherapy and RP in special cases. However,

the impact on urinary continence and erectile function preservation is still in question.[32]

Treatment for locally advanced disease

If there is biochemical recurrence after radical surgery (PSA > 0.2 ng/mL), therapies such as adjuvant or salvage radiation, monitoring or androgen deprivation can be offered. Hormone blockade is used as a palliative treatment in recurrent disease after radiation therapy. In the last decade, numerous studies have shown that hormone blockade, coupled with either of these therapies, can significantly increase the overall survival rate and decrease disease progression. However, castration is not without complications.[32,34]

Treatment for metastatic disease

Hormone blockade is the preferred therapy for metastatic disease, though it is not a curative treatment. Its goal is the deprivation of androgen sources by surgical castration (orchiectomy) or by suppression or pharmacological castration (anti-androgens, similar inhibitors or GnRH agonists). In addition, diethylstilbestrol (DES) is a "vintage" medication with distinctive characteristics (powerful central and peripheral mechanisms of action that grant increased bone protection) and a lower price compared with the aforementioned options. Its use has been limited because studies in the 1970s showed that a dose of 5 mg was associated with a substantial increase in cardiovascular and thromboembolic events, with questionable results and deficient methodology. However, in Europe and in our country, DES is used with good oncological results at doses of 1 and 2 mg every 24 hours, without significant cardiovascular or thromboembolic effects. Hormone blockade is primarily used in association with RT in high-risk patients or to control the disease in patients with metastatic PC. As previously mentioned, hormone blockade has functional and metabolic complications, including osteoporosis (except DES and bicalutamide), increased cardiovascular risk, gynecomastia, sexual dysfunction, obesity and sarcopenia (loss of muscle mass), which affect quality of life. Radiotherapy is also used to treat late PC complications, mainly bone metastases and gynecomastia.[32,34]

Treatment for hormone-refractory disease

When PC has progressed beyond hormone blockade, treatments based on second- or third-line chemotherapy (docetaxel, cabazitaxel) have shown not only effectiveness in reducing the number of metastases but also an increase in overall survival. A variety of medications can be used as monotherapy or in combination, such as enzalutamide, abiraterone, and radium-223. These medications show excellent results but have higher costs.[35]

Prevention

The aim of PC prevention with the use of medications is to decrease its incidence. Various agents that reduce PC development have been studied. The first was a double blind trial that studied the administration of finasteride or placebo [PCPT (Prostate Cancer Prevention Trial)]. In this trial, a 6.4% reduction in the incidence of PC was achieved with finasteride (5-□-reductase type 2 inhibitor). This agent blocks the transformation of testosterone into dihydrotestosterone and also ameliorates lower urinary tract symptoms (LUTS), resulting in lower surgery rates. However, in this study, PC diagnoses were histologically more aggressive, with more high-grade tumors (1.3%). In the second study, dutasteride (5-□-reductase type 1 and 2 inhibitor) was compared with a placebo [REDUCE (Reduction by Dutasteride of Cancer Events)]. A 23% reduction in PC incidence was achieved in this study, without any association with more aggressive PC. Moreover, reduced frequencies of PC have been reported with soy, lycopene, green tea and statin consumption, but these results are questionable. A recent study named SELECT (Selenium and Vitamin E Cancer Trial) did not show a reduction in PC risk. There is no doubt that PC is a disease with several unclear prevention targets (e.g., Metformin).[36] To date, compelling evidence exists only for medications that reduce PC incidence; there are no convincing data showing that a dietary supplement can achieve PC reduction. Finally, lifestyle changes, including exercise and diets low in saturated fat with increased antioxidants and omega 3 and 6 fatty acids, are healthy habits that can prevent PC and other comorbidities.[19]

Conclusions

Prostate cancer is a slowly developing disease. Early diagnosis with the advent of PSA screening has been beneficial, but overtreatment is also a reality. The PSA test has high sensitivity but low specificity. To date, we can predict PC evolution based on PSA, the Gleason scale and DRE results, but we cannot precisely predict whether the PC will be indolent or aggressive. The patient must be involved throughout the examination with or without PSA and DRE, as well as in the selection of the most suitable treatment, ranging from observation to more

radical treatments. The best therapeutic solution will be the one that provides survival with the best quality of life and can be supported by a multidisciplinary team.

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

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