Chapter 56

Epidemiological profile of patients with prostatic neoplasia at an oncological hospital of SUS, Brazil

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ABSTRACT
Objective: To identify the epidemiological characteristics of patients with prostate cancer and evaluate the treatment with Eligard® monthly, quarterly and semiannually according to efficacy and tolerance in HCM from January 2007 to July 2018. Methodology: Epidemiological, descriptive, retrospective, cross-sectional and quantitative research through the review of medical records . The population 932 patients with prostate neoplasia, treated at Cristiano Varella Foundation - HCM, MG state, Brazil, adult men (≥18 years old), with indication for Eligard® in monthly (7.5 mg) (n=115), quarterly (22.5 mg) (n=637) and semiannual (45 mg) (n=180) dosage. Results: Median age was 72 years (65-78). Median time since diagnosis was 8.5 months, with 598 (64.2%) of patients with a diagnosis of 12 months or less, and 158 (17%) with time since diagnosis of more than 4 years. The majority (63.4%) had low education, were married (69.9%) and non-white (66.41% black + brown). Regarding occupation, 541 (58.05%) are retired 148 (15.88%) and rural workers. Much of the information collected in the medical records about housing was not available 464 (49.8%), but 318 (34.12%) of the patients own their own homes. As for transportation, most 877 (94.1%) have the vehicles of the municipal health departments as their main means of transportation, which corroborates the information of low *per capita* income, low education, that is, low socioeconomic structure. All patients being treated at HCM with prostate cancer (100%) have support from the municipal health secretariats, the Basic Health Units, and also from the hospital itself. Regarding the nutritional status of patients, 754 (80.9%) have good nutrition (eutrophic), only 84 (9.02) were malnourished and 49 (5.22%) were obese. As for prevention (PSA exams), 444 subjects (42.4%) reported having had such an exam. Slightly more than 30% had a family history of cancer, and the same proportion for smokers and drinkers. Conclusions: Epidemiological characteristics (average age 75 years, non-white, married, with low education, retired, rural workers, depend on the support of the Health Departments of their municipalities, low *per capita* income, most have their own homes, are treated by SUS, do not smoke, do not drink, no family history); and clinical (most with stages II and III, treated with radiotherapy, comorbidities cardiovascular diseases, and adverse events considered the treatment itself). The results obtained allowed us to verify the efficacy of the hormone (Eligard®), a LHRH agonist used in the treatment of patients with this neoplasm, in all stages. The tolerability of the patients regarding this medication was also verified, with very satisfactory results in approximately 99% of all patients.

Keywords: Prostate neoplasms, Epidemiology, LHRH.

1 INTRODUCTION

Prostate cancer (PC) is the most common neoplasm among men in Brazil and worldwide, and its incidence has been increasing in recent decades. This is mainly due to two factors, the increase in life expectancy and the western lifestyle, characterized by high-calorie diets and sedentarism (LEITE; LOPES, 2007).

According to the *Global Cancer Statistics* (GLOBOCAN), with the exception of non-melanoma skin cancer, 19.3 million new cases of cancer and 9.9 million deaths are expected worldwide by the year 2020. PC has an estimated risk between 6.3 and 83.4/100,000 with the highest number in China and in Eastern European countries such as Belarus, Bulgaria, and Slovakia. In Brazil, in 2020, there were 98,000 new cases of PC (SUNG *et al.*, 2021). In 2019 in Brazil, it was the second type of cancer, with 15,983 deaths in men (BRAZIL, 2019). A study that analyzed survival in 71 countries found that in Brazil, this type of cancer had a 92.8% survival rate during the 2000-2004 quadrennium, 94.8% in the 2005-2009 quadrennium, and 94.1% in the 2010-2014 quadrennium (ALLEMANI *et al.*, 2018; BRAY *et al.*, 2018). For Brazil, the estimate for each year of the triennium 2020-2022 indicated the occurrence of 625,000 new cancer cases, non-melanoma skin will be the most incident (177,000), followed by breast and prostate cancers (66,000 each), colon and rectum (41,000), lung (30,000), and stomach (21,000) (BRASIL, 2020).

Prostate cancer is a public health problem in Brazil and is gaining relevance due to the epidemiological profile presented, and with this, the topic is gaining space on the political and technical agendas of all governmental spheres. Knowledge about the epidemiological aspects allows establishing priorities and allocating resources in a targeted way to positively change this scenario in the Brazilian population. Late diagnosis and, sometimes, inadequate therapy, contribute to the mortality of PC. When diagnosed in early stages, it has great chances of cure. It is a curative disease in early stages with radical prostatectomy or radiotherapy associated with hormone therapy. It is a hormone dependent pathology of androgen. Androgen deprivation therapy, has been considered the gold standard of treatment for decades, to suppress serum testosterone in management of hormone sensitive and castration resistant diseases, such as leuprorrelin acetate (Eligard)® (HUGGINS *et al.*, 1941; PORCARO et *al.*, 2016; OHLMANN; GROSS-LANGENHOFF, 2018).

However, clinical trials are limited by patient inclusion and exclusion criteria, and the need for "real world" data remains. In this research, data were pooled in a non-interventional study to investigate efficacy and tolerability of Eligard depot formulations® , monthly, quarterly, and semiannually, in a broad population of patients found in routine HCM clinical practice.

The interest in developing this research came from the need to know the epidemiological and clinical characteristics of PC in patients seen and assisted at the Muriaé-MG Cancer Hospital (HCM). The institution lacks local information about the disease, not only in the state of Minas Gerais, but also in the region it covers. Currently, it is frequently guided by information published in international studies due to the lack of research in Brazil in general and, especially in the Zona da Mata Mineira, a location considered to have a low socioeconomic and cultural index of patients with this neoplasm.

The notoriety of cancer as a disease that is among the leading causes of death in the world suggests that an in-depth approach to its intrinsic aspects of presentations and its regionally involved risk factors

should be pursued. Cancer is considered by the World Health Organization (WHO), a serious disease with high mortality.

In Brazil, there is a "National Policy of Integral Attention to Men" that recognizes the health problems of this population as a public health problem. This research is of fundamental importance, since knowing the lifestyle and health care seeking habits of men can subsidize strategic planning for health promotion, disease prevention, reduction of injuries, treatment and recovery and consequently improve the quality of life of these men and their families. So far, the epidemiological and clinical profile of these patients is not known, and whether their diseases are and/or maintain the same pattern as in other research centers. In the search for this knowledge, this study proposes to search for subsidies in order to delimit the profile of these patients and thus, constitute an element for special and directional attention in the assistance to patients, at the primary, secondary and tertiary levels of health care.

In these circumstances, one walks blindly about what the profile of these patients is and if there is anything different to be done in their treatment, taking into account the variability of treatments to offer. Knowing the pathophysiology of PC, it is known that it can take on average up to fifteen years to develop up to 1 cm^3 in size, this allows for hope and also brings responsibility to try to receive this patient in the early and curative stages of the disease. Although it is not possible to prevent the diagnosis of PC, it can be made early, and thus initiate treatment in order to save lives and prevent even greater suffering to these patients and their families.

Therefore, a study with information on the epidemiology and treatment provided to these patients from January 2007 to July 2018 was necessary in order to substantially improve the care of patients with prostate cancer.

Both in Brazil and worldwide there is a growing increase in the number of patients in routine outpatient treatment with this neoplasm and the change in Eligard posology® has been an excellent choice in daily clinical practice for the treatment of these patients, due to its convenience, efficacy, tolerability, accessibility, and cost according to the Unified Health System (SUS) table. Over 11 years of experience with the use of Eligard® , there was no change in PSA dosages. Thus, the patients were benefited in terms of return time (quarterly or half-yearly) for consultations, especially for the elderly, and those living at long distances from the hospital. Consequently, allowing the creation of new outpatient vacancies to care for other patients.

The main objective of this study was to identify the epidemiological and clinical characteristics of patients with PC and evaluate treatment with Eligard® monthly, quarterly, and semiannually according to efficacy and tolerance in the HCM from January 2007 to July 2018 by creating a database of patients affected by this neoplasm. Secondarily, a database was created with clinical and epidemiological information of patients with PC seen at HCM; to identify sociodemographic and clinical characteristics of

patients using Eligard® ; to evaluate the initial PSA, 6 months and 12 months after treatment with Eligard® monthly, quarterly and semiannually and the adverse effects during treatment with Eligard® .

2 PROSTATE CANCER (CP)

PC has been reaching increasingly higher population proportions, representing, among others, a major public health problem. Estimates in historical series are increasing in new cases and, consequently, deaths. Studies show that the incidence of this type of cancer is higher in developed countries compared to developing countries. It has been identified as a disease of aging, ie, it affects men over 65 years (STANGELBERGER *et al.*, 2008) and is the most common malignant neoplasm among older men (BECHIS *et al.*, 2011).

The risks of death from cancer have increased in recent years, according to Friestino *et al.* (2013), due to longevity and consequently, exposure to risk factors, by increasing urbanization and unhealthy daily habits. This increase in mortality has unique characteristics, for example, "the number of male deaths exceeds the female ones; for this reason, men can be pointed out as those who have a higher risk of dying from this cause" (FRIESTINO *et al.*, 2013).

Risk Factors

The occurrence of prostate cancer has peculiar aspects and specific risk factors, such as: advanced age (it mainly affects men over 50 years old); ethnicity (this tumor is about 1.6 times more common in black men when compared to white men); and genetic predisposition, in which the family history of a father or brother who had PC before the age of 60 years increases 3 to 10 times the chance of developing the disease compared to the general population (FRIESTINO *et al.*, 2013).

However, other risk factors should be considered common to different types of cancer, such as lifestyle and eating habits (GOMES *et al.*, 2008). In cases of prostate cancer some preventive measures should be taken, such as smoking, alcoholism, obesity and sedentary lifestyle, and as a protective factor has been recommended diet rich in vegetables, selenium, vitamins D and E, lycopene and omega 3 (BRASIL, 2002/2015).

Studies suggest other risk factors for PC, however, without conclusive evidence, under the influence of food consumption, sexual behavior patterns, alcohol consumption, exposure to ultraviolet radiation and occupational exposure to the development of PC. Obesity has also been associated with PC, with an association between high-grade disease and increased body mass index (BMI) (ROHRMANN *et al.*, 2003). Besides these, multiple factors are always involved in the development of PC, such as changes resulting in the proliferation and differentiation of the cells that make up the epithelium of the gland. The growth and maintenance of the normal prostatic epithelium are regulated by testosterone and vitamin D. Testosterone stimulates cell proliferation, while vitamin D inhibits it. Both pathways interact with the insulin-like growth

factor 1 (IGF-1) axis, and disturbances in them have been related to cancer (RUSSEL *et al.*, 1998; LEITE; LOPES, 2007).

In the pathogenesis of PC, testosterone diffuses into the cells of the epithelium and prostatic stroma, where it is reduced by 5-alpha-reductase to its most active form, 5-alpha-dehydrotestosterone (DHT). This binds to the androgen receptor, activating the target gene response and promoting cell proliferation. The androgen receptor has 8 exons, which is a member of the transcription factor family and is located on the long arm of chromosome Xq11-12. The PC is correlated with the polymorphism of this gene, and is also related to its greater or lesser predisposition to disease (GELMANN, 2002). Exon 1 contains the CAG repeat area, whose length is inversely related to the transcriptional activity of the target gene. Thus, the smaller the polymorphism area, the greater the sensitivity to androgen (LEITE; LOPES, 2007). This partially explains the higher incidence and severity of cancer in African Americans, because they have a short CAG sequence, and the lower incidence among Asians who have a long sequence and therefore are less affected by this type of cancer. Studies show that for each additional CAG repeat there is a corresponding 3% decrease in the risk of developing the disease (STANFORD *et al.*, 1997).

Genetic susceptibility plays an important role in several types of cancer, including prostate cancer, because it is an extremely heterogeneous disease with multiple *loci* that contribute to its susceptibility. The hereditary form may explain the large proportion of this disease among young men, occurring in 10% to 20% of PC cases. And demographic factors including age and dietary habits contribute to high incidence of the disease and currently PSA screening has clinically diagnosed 90% of patients with PC (ABESHOUSE et al., 2015).

Ethnicity has also been considered a risk factor for PC. The lowest incidence rates of this neoplasm are seen in Asian men, particularly in India, China and Japan. South Asian men living in England have a lower incidence of PC than their white counterparts (relative risk 0.8) (METCALFE *et al.*, 2008). Higher rates are observed in black men. African American men are believed to have 1.3-2.0 times the risk of developing CP than Caucasians, and black men (regardless of black-African or black-Caribbean origin) have a 3-fold higher risk of developing CP than white men (BEN-SHLOMO, 2009).

Religion was one of the variables observed in the analyzed medical records. However, few studies, place it as relevant in research, as in a study to characterize the epidemiological profile of men with cancer in the interior of São Paulo (RODRIGUES; FERREIRA, 2010).

Family history has been shown to be a risk factor for CP (GOH *et al.*, 2012). About 5-10% of cases are evaluated to have substantial inherited family component. It has been established that a large gene predisposition could account for up to 40% of cases of prostate cancers in younger men up to 55 years of age (ELO; VISAKORPI 2001). The patient has a relatively high risk with increasing number of first-degree relatives diagnosed and the likely risk from father to son being increased by 2.5-fold, while the relative risk among brothers is 3.4-fold (JOHNS; HOULSTON, 2003). Patients with hereditary CP are often diagnosed

6-7 years earlier than spontaneous cases (BRATT *et al.*, 2002). However, the evolution and progression of cancer of a certain grade and stage should be expected by observing tumor biology and can occur regardless of chronological age. The age-independent impact on CP-specific survival is not well established (STANGELBERGER *et al.*, 2008).

Age is one of the most prevalent risk factors for PC, with approximately 85% of cases diagnosed in men over 65 years and an approximate incidence of only 0.1% in those under 50 years. There is strong evidence that older men make up the high-risk group for PC and are prone to shorter survival time (STANGELBERGER *et al.*, 2008) .

Dietary habits also play an important role in promoting PC. The consumption of highly saturated fats, especially those present in red meat and dairy products, would be one of the predisposing factors for the development of cancer. Together with heterocyclic amines, achieved by cooking at high temperatures and prolonged ingestion of red meat, they seem to have a carcinogenic effect on the prostate. Some elements are highly protective, such as vitamin E, selenium, a high-fiber diet, and exercise. Studies show a decrease in the growth of PC tumor lines when in contact with the serum of individuals on a low-fat, high-fiber diet who exercised regularly. The intake of alpha tocopherol, one of the main components of vitamin E, present in large quantities in soy-rich foods, decreases five times the risk of developing PC in individuals over 50 years of age.

Several epidemiological studies use among others, variables to be surveyed, such as occupation, housing, marital status, unemployment in the family, regions, continuous expenses, family rearguard, transportation, support network (GONÇALVES *et al.*, 2008; RODRIGUES; FERREIRA, 2010; XIAO et *al.*, 2013; QUIJADA *et al.*, 2017).

As for occupation, it deserves to be highlighted, because especially in certain occupations, such as agricultural activities with exposure to pesticides, herbicides and fertilizers, which can increase the risk of disease by six times, machine shop, paper printing, plumbers and workers in the manufacturing industry of rubber or leather products (HAMAD; ABUIDRIS, 2011). Professionals who work in these activities are more vulnerable to PC due to direct and frequent contact with carcinogens and/or mutagens.

Prostate Cancer Screening

There is variation in incidence and mortality rates, mostly due to early diagnosis through the use of screening based on prostate-specific antigen (PSA). The variation in incidence among countries can be up to 24 times and mortality up to 10 times (BUSATO JÚNIOR; ALMEIDA, 2015).

A worldwide analysis of the incidence of PC divided the countries into six groups according to the rates per 100,000 inhabitants, pointing out a rather intriguing trend about the behavior of this disease. Countries such as USA, Australia, and Northern Europe are in the first group (83.2 to 173.7) in incidence and Brazil in the second (45.3 to 83.1). However, with regard to PC mortality rates, this trend is reversed.

The USA becomes part of the fourth group (7.5 to 11.5), while Brazil, Australia and Northern Europe remain in the second group with rates ranging from 15.3 to 22 deaths per 100,000 inhabitants (BUSATO JÚNIOR; ALMEIDA, 2015).

In most underdeveloped countries there is incomplete and precarious structure of the health system in the underreporting regarding incidence, treatments, complications, and mortality. In Brazil the few data are not reliable about the *screnning (*screening) of PC (SPCa) and, "the few decisions made are largely made from data obtained in other populations around the world, even with wide geographic and epidemiological variation among peoples worldwide" (BUSATO JÚNIOR; ALMEIDA, 2015, p. 116).

Studies evidence the lack of interest of the male population about PC, especially in the age group of 65 to 70 years old. A study conducted with 135 physicians aged ≥ 51 years at the Federal University of Minas Gerais (UFMG) showed that 21% of them have never had a PSA. In Brazil other studies indicate several reasons why men aged <70 years do not do PSA and digital rectal examination, among them, low education, per capita family income less than 0.5 minimum wages, factors that are clearly related to work activities, ignorance and difficult access to health care (MOYER, 2012).

Diagnosis

The following diagnostic methods are indicated for the identification or tracking of PC: digital examination of the gland, PSA dosage, transrectal ultrasonography, biopsy and histopathological study. The rectal examination associated with the PSA dosage demonstrates signs of PC, and pelvic or transrectal prostate ultrasonography is indicated. The results will indicate if there is (or not) the need to perform transrectal prostate biopsy. It is advisable to perform the biopsy when the PSA levels are higher than 4 ng/ml. However, the diagnosis will only be made after confirmation through histopathological study performed with the tissue sample obtained by prostate biopsy (BACELAR JÚNIOR *et al.*, 2015).

According to the *American Cancer Society* (2018), the PSA test is an important part of the research, staging, and monitoring of patients with PC. It is one of the first tests performed on men who have symptoms that they suspect may be caused by PC. The chance that a man will develop this type of cancer increases proportionally with the PSA level. Usually when PC is present the PSA level is >4 ng/mL. However, a level below this does not mean that the cancer is not present. Approximately 15% of men with PSA <4 ng/ml are diagnosed with PC on biopsy. Men with PSA levels between 4 ng/ml and 10 ng/ml have a one in four chance of having the disease. If the PSA is >10 ng/ml, the chance of CP is greater than 50% (*American Cancer Society*, 2018).

Approximately 70% of PC are visible on transrectal ultrasound, this sensitivity is similar to detection by rectal touch, PSA and nuclear magnetic resonance imaging (NMR) (JUREIDINI *et al.*, 2007).

The histological Gleason grading is universally used and is the most important single prognostic factor in PC. It takes into account tumor heterogeneity and consists of five patterns represented numerically

from 1 to 5. The sum of two patterns predominantly is the Gleason score that ranges from 2 to 10. The numbers that make up the sum must be informed in parentheses, the first being the one that predominates in the neoplasm. In homogeneous tumors, the numbering is doubled. The histological grading is based on the architectural conformation of the glands in their arrangement and growth characteristics, being used mainly to choose the most appropriate therapy (LEITE; LOPES, 2007).

Through an analysis of PSA level, Gleason score by biopsy and clinical stage, it is possible to define low-, intermediate- and high-risk disease in terms of progression after definitive local therapy. High-risk characteristics include PSA level greater than 20ng/ml, Gleason score of 8 to 10, or clinical stage of T2a or higher (GOMELLA, 2005).

Table 1 shows the risk definition and staging criteria adopted: **Very Low Risk**: T1c stage, Gleason score less than or equal to 6, PSA less than 10 ng/mL, less than three positive biopsy specimens, less than or equal to 50% involvement in each specimen, and PSA density less than 0.15 ng/mL. **Low risk**: T1-2a staging, Gleason score up to 6 and PSA up to 10ng/ml. **Intermediate risk**: stage T2b or T2c or Gleason score 7 or PSA of 10 to 20 ng/ml. **High risk**: stage greater than or equal to T3 or Gleason score greater than or equal to 8, or PSA greater than 20 ng/ml.

For very low and low risk patients, there is no indication for bone scintigraphy or computed tomography (CT). The only exceptions include bone symptoms, abnormal physical examination findings, or elevated serum alkaline phosphatase (ALP) levels. Nuclear magnetic resonance imaging (MRI) is suggested, preferably in patients considered for active surveillance.

For patients at intermediate risk, bone scintigraphy is optional in cases of asymptomatic individuals with normal AF. It is mandatory in patients with bone symptoms or elevated AF. CT or MRI is optional.

For high-risk patients: bone scan and CT or MRI of the pelvis are recommended. MRI is indicated for high-risk patients who are potential surgical candidates.

There is no standardization regarding the staging of patients with biochemical recurrence and low PSA values after radical prostatectomy (RP) and radiation therapy (RT). Proton emission tomography and computed tomography (PET/CT) or PSMA 68-Ga (prostate specific membrane antigen - Gallium 68). These two tests are not usual in clinical routine because they are high cost, without SUS coverage, being used in specific situations (SCHUTZ *et al.*, 2015; BUZAID; MALUF, 2015). (Table 1).

Table 1. Localized prostate cancer: biochemical recurrence risk (D'Amico Classification)

	(a) Low risk	(b) Intermediate risk	(c) High risk	Indicated Exams
Clinical Stage	Up to T2a	T2b	T2c-T3a	Laboratory examinations
Gleason score (c)	Up to 6	7	Above 7	Laboratory tests, plain chest X-ray and bone scintigraphy
Serum PSA (ng/ml)	Below 10	Above 10 and below 20	Above 20	Laboratory tests, simple chest X-ray, bone scintigraphy and Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of abdomen and pelvis

(a) Low risk implies all criteria.
(b) A single criterion present is sufficient to consider high risk.
(c) The Gleason score is based on two of the patterns found in the microscopic examination of the prostate: one, called the primary pattern, represents the largest part found and is classified into 5 grades of differentiation; the other, the secondary pattern, represents the smallest part found and is also classified into 5 grades. The sum of the respective grades gives the Gleason score.
Source: D'Amico, 2002.

Based on these criteria patients are classified into very low, low, medium and high risk for developing CP according to biopsy data, PSA, Gleason score and staging exam (SCHUTZ *et al.*, 2015).

At diagnosis, the pathologist classifies the Gleason score, which ranges from 2 to 10, and grades the two most frequent areas of the tumor from 1 to 5. The lower the Gleason score, the better the patient's prognosis. Scores between 2 and 4 mean that the cancer is likely to be slow growing. Intermediate scores, between 5 and 7, can mean either slow-growing or fast-growing cancer, and this growth will depend on a number of other factors, including the length of time the patient has had the cancer. Scores at the bottom of the scale, between 8 and 10, mean very fast growing cancer (BRASIL, 2002, p. 14).

The treatment must be individualized for each patient, taking into consideration the patient's age, tumor staging, histological grade, prostate size, comorbidities, life expectancy, the patient's wishes, and the available technical resources (BRASIL, 2002).

Staging

The staging of prostate adenocarcinoma to define the stage of disease is determined by the International Union Against Cancer (UICC), using the following criteria: T (tumor), N (lymph node) and M (metastases) and histopathological grading using the Gleason score (Tables 2 and 3).

Table 2. Tumor Node Metastasis (TNM) classification for PC

T - Primary tumor		
	Tx	The primary tumor cannot be evaluated
	T0	No evidence of primary tumor
T1	Tumor not clinically palpable or visible by imaging method	
	T1a	Tumor incidence - histopathological finding in <5% of resection tissue
	T1b	Tumor incidence - histopathological finding in >5% of resection tissue
	T1c	Tumor identified by needle biopsy (elevated PSA)
T2	Tumor confined to the prostate	
	T2a	Tumor encompasses half of one lobe or less
	T2b	Tumor encompasses more than half of one lobe, but not both lobes
	T2c	Tumor encompasses both lobes
T3	Tumor beyond the prostatic capsule	
	T3a	Extracuplar extension (unilateral or bilateral)
	T3b	Tumor involves the seminal vesicle (one or both)
T4	Tumor fixed or invades adjacent structures besides the seminal vesicles: bladder neck, external sphincter, rectum, levator muscles or pelvic wall	
N - Regional lymph node involvement		
	Nx	Regional lymph nodes not evaluated
	N0	No metastases to regional lymph nodes
	N1	Regional lymph node metastases
M - Distant metastasis		
	Mx	Distant metastases not evaluated
	M0	Absence of distant metastasis
	M1	Distant metastasis
		M1a - Non-regional lymph nodes
		M1b - Bones
		M1c - Other organs

Source: SCHUTZ *et al.*, 2015, pp. 448-449.

Table 3. TNM grouping

Stage I	T1a-2aN0M0G1
Stadium IIA	T1a-2bN0M0G1-G2
Stage IIB	T2cN0M0qqG or T1-2N0M0G3
Stage III	T3N0M0qqG
Stage IV	T4N0M0qqG or qqTN1M0qqG or qqTqNM1qqG

Source: SCHUTZ *et al.*, 2015, p. 448.

However, according to the Ministry of Health, in its guidelines, it states that there is no evidence that treatment of early-stage tumors has effectiveness that supports the risks of adverse effects (BRASIL, 2014b; BRASIL, 2014c).

Treatment

The treatment of localized PC is still controversial, regardless of the risk group. These controversies arise from the biological characteristics of this neoplasm and the relative heterogeneity of its natural history. There are no unique patterns of tumor evolution in the different grades, stages, and risk groups. Generally, "patients with low-risk tumors evolve favorably regardless of the treatment chosen, while those with medium- and high-risk tumors tend to have higher recurrence rates" (ARAP *et al.*, 2007, p. 43).

There are several therapies that can be employed, such as radical prostatectomy, transurethral resection (TUR), a urethral procedure to remove (tunneling) obstructive prostate tissue, external conformal radiotherapy, brachytherapy, chemotherapy and hormone therapy, and watchful observation, an option for

localized disease, and this procedure should be used in patients over 75 years of age, with low histologic grade tumors and limited life expectancy (ARAP *et al.*, 2007).

In radiotherapy of localized CP there are several types, such as brachiotherapy or external and internal radiotherapy, using permanent or temporary radioactive implant; external radiotherapy techniques (conventional or three-dimensional - conformal, intensity modulated, guided or not by imaging during treatment) and internal (low dose rate, high dose rate) and forms of application (isolated or combined) (BRASIL, 2015). However, hypofractionated and ultrahypofractionated external radiotherapy, stereotactic radiotherapy (fractionated radiosurgery) and real-time planning (intraoperative) still need more consistent studies to be established as a good therapeutic practice for PC.

The different techniques of three-dimensional external radiotherapy rely on specific planning systems after CT or MRI image acquisition, seeking to allow the organs and the tumor target to be delineated and addressed with dose optimization within the tolerance limit of the organs close to the tumor target, which receives the dose required for disease control.

"*Inverse planning*" (*inverseplanning*) arose out of concern about the dose applied to normal tissue. The use of inverse planning is specific to intensity-modulated radiation therapy (IMRT). The standard dose per fraction is 1.8 to 2 Gray (Gy), totaling 70-74 Gy, divided into 5 fractions per week for 7 to 8 weeks. Dose escalation is increasingly proposed and corresponds to a dose of 76-80 Gy or more. This high dose is only possible by the use of IMRT, provided the toxicity is acceptable (D'AMICO, 2002; BRASIL, 2015).

External radiotherapy is one of the treatment options for clinically localized PC and can be indicated for all three D'Amico prognostic groups (Table 1), alone or in association with hormone therapy, according to staging.

The organs at risk of late toxicity are mainly the rectum, the bladder and to a lesser extent the femoral heads. Radiotherapy techniques have evolved to allow higher doses to be delivered safely from three-dimensional (3D) planning. For example, three-dimensional conformal radiotherapy (TCT-3D) has replaced the previous, two-dimensional one, with demonstration of being less toxic by a randomized trial (DEARNALEY *et al.*, 1999).

There is more than one therapeutic alternative for the treatment of localized prostatic adenocarcinoma, depending on its biochemical recurrence risk category (isolated PSA increase). Radiation therapy can be considered in all of them. D'Amico's risk classification (Table 1) is the most widely used to guide the choice of the most appropriate option.

androgenic suppression: surgical castration (bilateral orchiectomy) or chemical castration (drug hormone therapy) with agonist/antagonist of the luteinizing hormone-releasing hormone - LHRH, associated with radiotherapy for cases in more locally advanced and high-risk stages. In addition to these cases, neoadjuvant (previous) hormone therapy can be indicated for three months before the beginning of radiotherapy with

the objective of reducing the prostate volume in patients who present with a voluminous prostate, regardless of the risk group to which they belong.

Patients presenting with biochemical recurrence (RB) with a pattern compatible with probable local recurrence post-radical prostatectomy (RRP) "have an indication for treatment with external salvage or rescue radiotherapy (RTSalv), in order to provide greater long-term disease control" (BRASIL, 2015).

The use of chemotherapy for PC is restricted to the treatment of advanced metastatic disease refractory to hormone therapy, and its initiation is usually indicated when such patients become symptomatic, emphasizing that when chemotherapy is indicated, hormone therapy should not be suspended (NCCN, 2015; BRASIL, 2015).

However, to date, the best choice for the treatment of PC has been surgical, performed through radical prostatectomy, which is indicated by the literature as the only form of treatment with reduced specific and overall mortality and reduced risk of disease progression proven in controlled and randomized study (BRASIL, 2015).

The patient's age should not be the only criterion to be adopted for life expectancy, because this evaluation is subjective and usually difficult to perform. Some patients with advanced age may have good clinical and surgical conditions, while other younger patients may suffer from multiple comorbidities. "For these reasons, the age and health of the patient, the characteristics of the cancer, the possibilities of cure with treatment, and the risks of complications influence the indication of treatment" (ARAP *et al.*, 2007, p. 43).

The advantages of radical surgery over radiotherapy lie in the better long-term cure rates, the ease of detection and treatment of recurrences, the low mortality of modern surgical techniques, the possibility of salvage radiotherapy, and the ease of postoperative follow-up (undetectable PSA) (ARAP *et al.*, 2007).

Androgen Deprivation Therapy is used in all stages of the disease, from the earliest, biochemical relapse after prostatectomy or radiotherapy, and can be given as monotherapy or as part of a multimodal approach system (HUGGINS *et al.*, 1941; PORCARO *et al*, 2016; OHLMANN; GROSS-LANGENHOFF, 2018). The most frequently used ADT (*Androgen Deprivation Therapy*) is LH-RH (*Luteinizing Hormone Releasing Hormone*), such as Eligard® (LA), a long-acting luteinizing hormone-releasing hormone agonist well tolerated by patients, and with proven efficacy (MOROTE *et al.*, 2007).

LH binds to specific receptors on the *Leydig* cell membranes of the testis and stimulates testosterone production. Administration of continuous high doses of LHRH or potent LHRH agonists results in a marked reduction of gonadotropin controlling the hypothalamic-pituitary system where luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are released (FRANCO; SAUHAMI, 2015), in the first moment induce testicular testosterone production, leading to initial transient testosterone increase (e.g., "*flare*") (OHLMANN; GROSS-LANGENHOFF, 2018).

The negative *feedback* created by chronic LHRH agonist exposure, resulting in negative regulation of LHRH receptors and suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion, causing testosterone reduction, traditionally defined as <50 ng/dL, although more recently redefined as <20 ng/dL, within 2 to 4 weeks of treatment initiation. Most patients achieve castration levels of testosterone at levels typically achieved after bilateral orchidectomy (MOTTET *et al.*, 2011; Mottet *et al.*, 2016).

Originally, LHRH agonist treatment requires subcutaneous injections, in the following formulations: monthly (7.5mg), quarterly (22.5mg) and, semiannually (45mg) approved on the pharmacological market (CHU *et al.*, 2002; CRAWFORD *et al.*, 2006; OHLMANN; GROSS-LANGENHOFF, 2018). All formulations of Eligard® (LA) (OUZAID; ROUPRET, 2011; BRAECKMAN; MICHIELSEN, 2014) are proven effective in reducing testosterone and prostate specific antigen (PSA) levels being well tolerated in patients in the various clinical studies (CHU *et al*, 2002; CRAWFORD et *al.*, 2006; OUZAID; ROUPRET, 2011; TUNN, 2011; MOTTET *et al.*, 2016).

However, studies have shown increased risk of diabetes *mellitus* and coronary artery disease with LHRH agonist use. In this context, a recent meta-analysis compared the incidence of cardiovascular events or death in six randomized trials with 2,328 patients with CP, comparing LHRH agonist "versus" LHRH antagonist for more than one year. It was observed in these studies, that individuals treated with LHRH antagonists had a lower risk of cardiovascular events (2.7 vs. 4.4%). Given this, the results suggested that patients with cardiovascular co-morbidities should be treated with LHRH antagonist (SCHUTZ *et al.*, 2015). Another case-control study including 10,250 with CP who received hormone suppression treatment (including LHRH agonist, oral antiandrogens, combined blockade, bilateral orchiectomy or estrogens) was observed to have an increased risk of developing acute renal failure with medications that suppress testosterone levels (LAPI *et al.*, 2013).

Although ADT has shown its benefit in treating patients with CP, serious adverse events can happen during treatment (PERLMUTTER; LEPOR, 2007). Specifically ADT reduces the risks of testosterone leading to hypogonadal condition and this would change the metabolic conditions of patients such as, dyslipidemias and hyperglycemia and increased body fat mass (BRAGA-BASARIA *et al.*, 2006). With respect to the renal system, hyperglycemia and dyslipidemia can disrupt glomerular and interstitial tubular membrane function. However, with testosterone decreased to the castration level, ADT could antagonize the effects of renal vasodilation, while at the same time creating an estrogen deficiency, which can negatively affect renal tubular function (HUTCHEN *et al.*, 2012). So, possibly, this is the mechanism that ADT use can increase the risk of renal injury (LAPI *et al.*, 2013).

In very low- and low-risk patients, there is individual discussion with the patient, and there are three therapeutic options of equal effectiveness, of different modalities and side effects: radical prostatectomy, external radiotherapy or brachytherapy, or active surveillance.

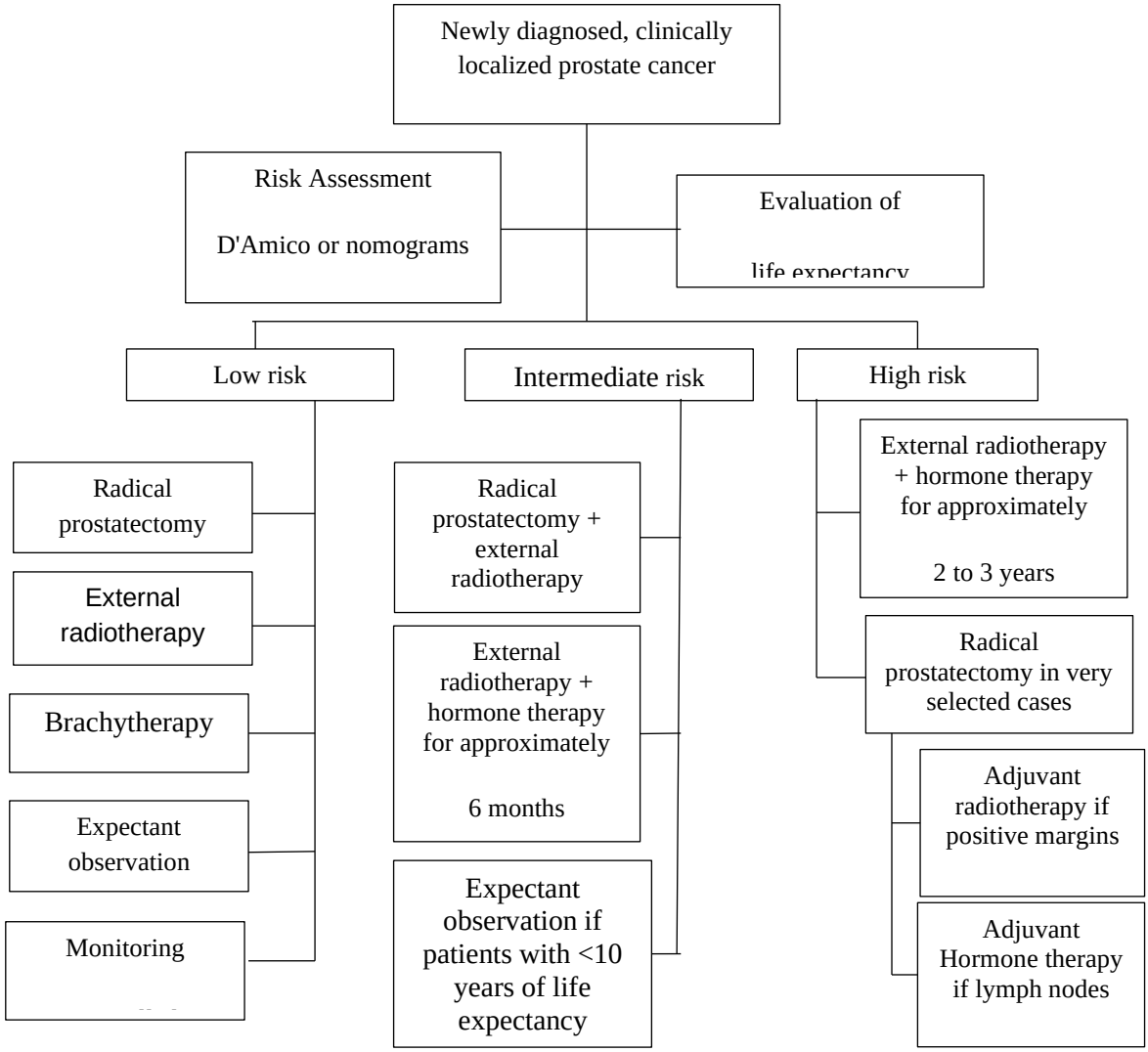
Intermediate risk patients: there are two therapeutic options: radical prostatectomy with extended lymphadenectomy or external radiotherapy at high dose or associated with short-term hormone therapy (LHRH analog for 4-6 months, neoadjuvant (prior) or concomitant/adjuvant) with possible booster dose in the prostate by brachytherapy. Favors radiotherapy alone in patients with relevant comorbidities and/or advanced age. In those symptomatic patients not candidates for local treatment (PR or RT) consider treatment with LHRH agonist or antagonist.

In high-risk patients, there are also two therapeutic options: external radiotherapy (with dose escalation and pelvic irradiation) and long-term hormone therapy (LHRH analog for 3 years, neoadjuvant (prior) and concomitant/adjuvant or radical prostatectomy with extended lymphadenectomy, reinforcing the need for radical resection with a negative margin, especially in young individuals with only one risk factor. In patients with positive margin and/or extracapsular extension and/or seminal vesicle involvement, lymph node involvement after prostatectomy favors adjuvant radiotherapy with use of LHRH agonist or antagonist (SCHUTZ *et al.*, 2015; BRASIL, 2015).

In biochemical recurrence (RB) after RP, external salvage radiotherapy with the use of LHRH agonist or antagonist is recommended. In RB after RT, the type of treatment is defined according to the initial tumor characteristic, as well as the PSA doubling time (greater or less than 10 months), PSA value and life expectancy at the time of recurrence (Figure 1).

In castration-sensitive high-volume metastatic disease chemotherapy associated with one of the LHRH agonists is favored. Low volume disease recommends suppression of continuous testosterone levels by medication (LHRH agonist or antagonist) or surgery (orchiectomy) with or without peripheral non-steroidal antiandrogen (SOUZA *et al.*, 2015). And in castration resistant, peripheral antiandrogen is withdrawn. If there is no response with withdrawal or progression, consider other drugs.

Figure 1: Organogram of locally localized disease management



Source: D'AMICO *et al.*, 2002.

3 METHODOLOGY

This is an epidemiological, descriptive, retrospective, cross-sectional research with a quantitative approach through chart review, conducted between January 2007 and July 2018. This study was approved by the Ethics Committee on Human Research of Santa Casa de Belo Horizonte, Minas Gerais, CAAE 94043618.3.0000.5138.

The sample: 1890 patients with prostate neoplasia, treated with hormone therapy in the same period, at HCM, MG, Brazil. From this total, 932 adult male patients (≥18 years old), with indication for Eligard® in monthly (7.5 mg) (n=115), quarterly (22.5 mg) (n=637) and semiannual (45 mg) (n=180) dosage were evaluated. Total serum PSA levels were measured at baseline and every 3 months, 6 months, and 12 months. Unfavorable events were assessed by medical records in the medical records at each patient clinic visit.

Variables studied: sociodemographic (age, marital status, education, ethnicity/race, religion, profession, housing, unemployment in the family, mesoregions of the state of MG and other states of the federation, continuous expenditure with some treatment, family support, transportation, available support

network, smoker, drinker, family history, health plan) and clinical variables from physical and electronic medical records; clinical (nutritional status, preventive, Gleason value (Differentiation), stage of PC and treatments).

Patients included in the study: hormone-sensitive PC diagnoses, with indication for androgen suppression therapy, regardless of PSA, Gleason value or tumor staging. Excluded patients: no information on initial PSA and 6 and 12 months after the start of Eligard . ®

Statistical analysis: data were tested for Normality by the Kolmogorov-Smirnov test. Comparisons of serum PSA levels at baseline, 6 months and 12 months by Friedman's test. Multiple comparisons by Wilcoxon's test. The significance level adopted for the tests was 5%. The statistical analysis was performed using the SPSS software version 22.0.

4 RESULTS

Patient Characteristics

Data from 932 patients were collected by a clinical oncologist. The general characteristics of the patients are shown in Table 4. The median age was 72 years (65-78). The median time since diagnosis was 8.5 months, with 598 (64.2%) of patients with a diagnosis of 12 months or less, and 158 (17%) with time since diagnosis of more than 4 years. The majority (63.4%) had low education, were married (69.9%) and non-white (66.41% black + brown). Regarding occupation, most 541 (58.05%) are retired and rural workers 148 (15.88%).

Most of the information collected in the medical records about housing, 464 (49.8%) was not available. 318 (34.12%) lived in their own house, 85 (9.1%) rented, and 51 (5.5%) lent. As for the others, they were distributed among home financing, nursing home, and cohabitation.

Unemployment is an important data, considering the current Brazilian scenario, with millions of unemployed. However, the research showed the opposite, because 312 (33.47%) of the patients reported being employed. However, this data must be viewed with attention, because 479 patients (51.40%) did not have this information in the analyzed medical records.

Most patients, 877 (94.1%), have as their main means of transportation the vehicles of the municipal health secretariats, which corroborates the information of low per capita income, low education, that is, low socioeconomic structure. All patients being treated at HCM with this neoplasm (100%), have support from the municipal health secretariats, the UBS and also from the hospital itself.

Regarding the patients' nutritional status, 754 (80.9%) presented good nutrition (eutrophic), only 84 (9.02) presented malnutrition and 49 (5.22%) were obese. As for prevention (PSA exams), 444 subjects (42.4%) reported having had such an exam. Slightly more than 30% had a family history of cancer, and the same proportion for smokers and drinkers.

The percentages of 'no information' data are lower due to the Hospital Cancer Registry (HCR), which is a mandatory database for all hospitals indistinctly. The HCM maintains the RHC sector active, maintaining the most reliable information possible, thus contributing to the lowest rate of unreported data. The HCM is a philanthropic institution, therefore justifying that almost all patients are treated with SUS resources (902, 96.7%).

Table 4. Sociodemographic characteristics of the study patients (n=932)

	n	%
Age in years (median; P25-P75)	(72; 65-78)*	
Time from first diagnosis (months/median)	(8,5;5-26)*	
Marital Status		
Married	652	69,9
Widower	116	12,4
Single	106	11,5
Divorced	58	6,2
Education		
No literacy	228	24,5
Elementary School	591	63,0
High School	60	6,4
Higher Education	16	1,7
No information	37	4,0
Ethnicity/race		
White	307	32,95
Brown	205	21,90
Black	414	44,5
No information	6	0,65
Religion		
Catholic	713	76,50
Evangelical	140	15,03
Spiritist	6	0,65
Other	62	3,0
No information	11	1,19
Profession		
Retirees	541	58,05
Rural Workers	148	15,88
Driver	31	3,32
Bricklayer	25	2,7
Trader	19	2,05
Public Employees	11	1,18
Autonomous	8	0,86
Vigilante	5	0,53
Electrician	5	0,53
Carpenter	5	0,53
Butcher	4	0,42
Engineers	3	0,33
Other	127	13,62
House		
No information	467	50,15
Homeownership	318	34,12
Rented	85	9,1
Ceded	51	5,5
Financing your own home	3	0,35
Asylum	2	0,25
Cohabitation	2	0,25
Other	2	0,25
Unemployment in the family		
Yes	141	15,13

No	312	33,47
No information	479	51,40
Continuous spending on some treatment		
Yes	232	24,9
No	251	26,9
No information	449	48,2
Family Rearguard		
Yes	482	51,72
No	9	0,96
No information	441	47,32
Transportation		
Own	39	4,2
* SMS	877	94,1
Other	16	1,0
Smoker		
No	490	52,6
Yes	330	35,4
No information	112	12,0
Ethylist		
No	550	59,0
Yes	258	27,7
No information	124	13,3
Family history		
Yes	301	32,30
No	495	53,11
No information	136	14,59

Source: Author, 2018.

The clinical characteristics are shown in table 5. The median Gleason value was 7 (6-8). There was a balanced distribution in relation to their classification, approximately 30% of tumors are high grade, with a similar proportion for low and intermediate grade. As for the stage, the predominance, 369 cases (39.5%) was of stage II, initial disease, possible cure, due to advances in medical techniques and greater routine of screening tests such as PSA, which justifies such an index. Moreover, such information is confirmed by the number of preventive exams (PSA) performed. However, the stages III and IV added up to a total of 487 patients representing 52.4% with advanced disease, which corresponds to the Brazilian reality.

The treatments for PC are surgical and non-surgical, but the treatment of choice is radical prostatectomy and radiotherapy according to the stage of the disease and age, observing comorbidities (blood pressure, diabetes mellitus, among others). Of the 932 patients, only 163 (17.5%) underwent radical prostatectomy, and most 588 (63.1%) underwent radiotherapy. Among the patients who underwent radical prostatectomy and transurethral resection (TUR), 19 also underwent bilateral orchiectomy as a form of hormone-blocking treatment. All patients underwent LHRH hormone therapy (Eligard®), regardless of the treatments they underwent, except those who underwent orchiectomy 19 (2.03%).

Table 5. Clinical characteristics of the study patients

	n	%
Nutritional status		
Caquexia	1	0,17
Chronic malnutrition	4	0,42
Mild malnutrition	18	1,93
Severe malnutrition	1	0,10
Moderate malnutrition	5	0,54
Malnourished	84	9,02
Eutrofic	754	80,90
Obesity	49	5,22
No information	16	1,70
Preventive		
Yes	444	47,6
No	395	42,4
No information	93	10,0
Gleason Value (Differentiation)		
Gleason value (median)	7	(6-8)*
Gleason score	n	%
Bass	320	34,4
Intermediate	318	34,2
High	274	29,3
No information	20	2,1
CP Stadium		
Stage I	35	3,7
Stadium II	369	39,5
Stage III	269	28,9
Stage IV	218	23,5
No information	41	4,4
Treatments		
Surgical Treatments		
Radical Prostatectomy	163	17,5
TUR (Transurethral Resection)	72	7,7
*Orchiectomy	(19)	2,03
Non-surgical treatments		
Radiotherapy	588	63,1
Chemotherapy	52	5,5
No information	57	6,2
**Hormone therapy	932	100

Source: Author, 2018

Bone metastases were recorded in 2.1% of the patients, while 2% had other distant metastases and 1.4% had lymph node metastases. At the beginning of the study, 43.8% of the study population had comorbidities, and 6.8% had no information available in the medical record regarding any existing comorbidity. Most of these comorbidities were cardiovascular diseases (85%). Overall, 76.3% of all patients met received concomitant medications. A total of 129 (13.8%) of the patients had received prior hormone therapy for the underlying disease.

Indication for Therapy with Eligard Formulation ®

Approximately 52% of patients had locally advanced PC, the main reason for starting treatment with Eligard® . Of 932 patients, 115 (12.3%) used Eligard® monthly; 637 (68.4%) quarterly, and 180 (19.3%) semiannually. Biochemical relapse after prostatectomy occurred in 104 (42.8%) of the 243 patients

who underwent prostectomy, and in 122 (20.7%) of the 588 who underwent radiotherapy. Among the 932 patients, 86.2% were treated with Eligard® monotherapy, while 13.8% of patients received Eligard® with an anti-androgen (bicalutamide, 8.4%; flutamide, 4.8%; cyproterone acetate, 0.6%).

Table 6 presents the median and the interquartile range (IQ) of PSA for the data set. Because the data show great variability, comparisons were based on the median. Median serum PSA levels were reduced by 99.7% from 25.6 to 0.08 ng/ml 12 months after the baseline visit for monthly LA (Figure 2). Results were comparable for the 3- and 6-month LA depot formulations, with reductions in median PSA level of 99.7% from 28.8 to 0.09 ng/ml and 99.8% from 23.2 to 0.04 ng/ml 12 months after the baseline visit, respectively. All comparisons were statistically signficant.

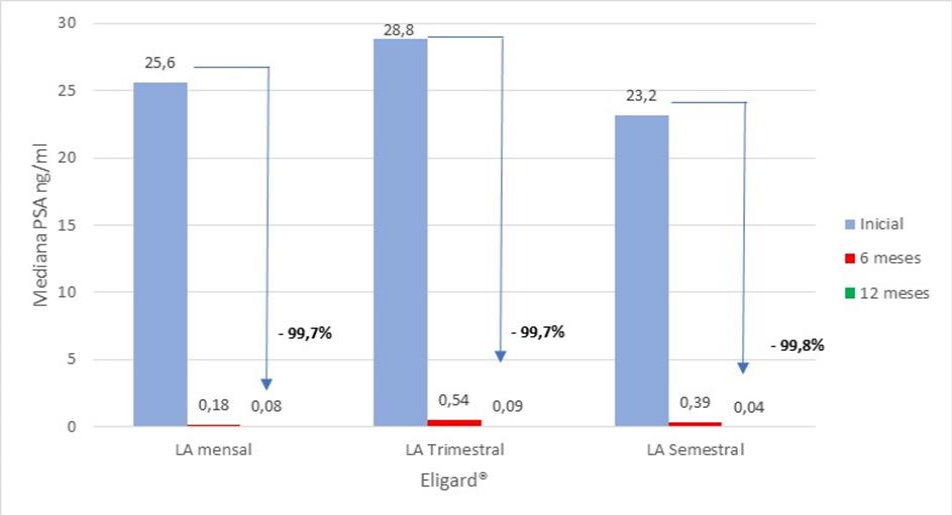
Table 6. HT 1st Line Treatment

HT Treatment 1st Line	PSA (median: P25;P75))			p* value
	Home	6 months after HT	12 months after HT	
Eligard® Monthly	n=115	n=108	n=104	<0,001
	25,60 (13,70; 86,0)	0,18 (0,05; 1,63)	0,08 (0,12; 0,70)	
Eligard® Quarterly	n=637	n=588	n=512	<0,001
	28,8 (13,0; 87,0)	0,54 (0,05; 3,59)	0,09 (0,01; 1,0)	
Eligard® Biannual	n=180	n=151	n=103	<0,001
	23,2 (9,44; 70,50)	0,39 (0,04; 2,08)	0,04 (0,01; 0,37)	

*Friedman's test
Source: Author, 2018.

Multiple comparisons (Wilcoxon test) showed significant differences, i.e. PSA was different in the initial period and 6 months (p<0.001), as well as in the initial period and 12 months (p<0.001) after medication use for all formulations. Only for the monthly formulation there was no statistically significant reduction from 6 months to 12 months of treatment (p=0.238).

Figure 2. PSA levels during treatment with the 1-, 3- and 6-month Eligard® (LA) formulation. Mean serum PSA levels were measured at baseline and at 6 months and 12 months after treatment initiation.
Source: Author, 2018.



Safety and tolerability

A total of 72 (7.7%) patients had non-severe adverse events reported being, sexual impotence (58; 6.2%) and hot flashes (23; 2.5%). These adverse events were considered by the clinical oncologist to be related to treatment with Eligard®(LA).

Serious adverse events (SAEs) occurred in 9 (0.096%) patients, being cardiovascular adverse side effects: stroke (n=2), hemorrhagic stroke, coronary heart failure, peripheral vascular failure, angina, PTE, and AMI (n = 1/each).

No patient discontinued treatment prematurely due to the mentioned events, including general weakness, fatigue, sweating attacks and local swelling after Eligard® (LA) injection. To date, 70.9% of patients are alive, 16.6% lost to follow-up, and 12.4% have died.

5 DISCUSSION

The median age of patients in this study was compatible with the age of men with PC evaluated in other studies (STANGELBERGER *et al.*, 2008; BECHIS et al., 2011; FRIESTINO *et al.*, 2013). Both retrospective and prospective studies show that PC is a disease that affects men of "old age", and, according to the National Cancer Institute, as in other cancers, "age is an important marker, gaining special significance in this neoplasm, since both the incidence and mortality increase exponentially after the age of 50 years" (BRASIL, 2002).

Marital status, the proportion of married men was higher than the others (widowed, single and divorced). Most had low education, less than high school, a result similar to other studies (MOYER, 2012) and possibly this fact is due to lack of knowledge and information about the disease.

In the ethnicity/race predominance of the black race, coinciding with most previous studies that point black men over 65 years with higher incidence of PC in relation to white and brown people (CRAWFORD, 2003; BEN-SHLOMO, 2009). However, Xiao *et al.* (2013) report that black men do not receive optimal treatment for this neoplasm, which worsens the health status of this population.

The Catholic religion was predominant, followed by the evangelical and other religions. A study by Rodrigues and Ferreira (2010) on the epidemiological profile of PC in the interior of São Paulo showed that the Catholic religion was the most prevalent among the study population, followed by the evangelical and other religions. Evaluating the profession, most men with PC treated at HCM are retired, followed by rural workers, and other professions, with these results being similar to other studies already published. This variable is not relevant in previous studies. However, Gonçalves *et al.* (2008), pointed out that the information contained in medical records about the profession exercised by these retirees, could be more consistent, since such an association would give a significant contribution, "to consolidate and/or substantiate risk factors." Likewise, other variables such as housing (50.15% without information), unemployment in the family (51.40% without information), regions, continuous expenses with some

treatment (48.2% without information), family rearguard (47.32% without information), among others of social, demographic and economic nature, because this information would be of paramount importance to determine appropriate policies and strategies in the preliminary intervention in the treatment of PC (XIAO *et al.*, 2013; QUIJADA *et al.*, 2017).

Practically all patients use transportation provided by the SMS, due to lack of resources to get around. The others benefit from the help of relatives and few use their own vehicles. This result corroborates the fact that the hospital's attendance is practically of patients coming from the SUS. One notices that in relation to the available support network, the indicators are practically identical to the previous item, i.e., almost 100% of patients rely on the support of the Municipal Health Secretariats of their municipalities, which presumes a lack of resources for PC treatment.

Smoking is one of the risk factors for PC, as for other types of cancers. Contrary to the majority of reports in previous studies, in this study, when analyzing the medical records, it was found that most men affected by this neoplasm reported that they were not smokers. If only the valid data are considered (excluding those without information), smokers are still lower than nonsmokers. These results are equally distributed with respect to alcohol drinkers, since most of the medical records report men who are nonsmokers. These two factors potentiate the disease. Tobacco consumption due to the presence of nitrosamines present in smoke (FRIESTINO *et al.*, 2013; FERNANDES et *al.*, 2014; BRASIL, 2018) and alcohol presents, in its metabolism, metabolites with both initiating and promoting effects in the process of carcinogenesis (SCHWARTSMANN, 2006).

Family history is considered a relevant risk factor in cases of cancers such as prostate cancer. In the analyzed medical records, most indicated that they had a family member with a history of cancer, and this was the most prevalent. However, the literature is still controversial regarding lower and higher aggressiveness of cancers in the family and sporadically CP (ELO; VISAKORPI 2001; CRAWFORD, 2003; JOHNS; HOULSTON, 2003; GOH *et al.*, 2012).

Practically all men with PC seen at HCM are treated with SUS resources. This result portrays the socioeconomic conditions of this population, i.e., they are retired, rural workers, underemployed, low education level, among other characteristics (QUIJADA et al, 2017).

The result of nutritional status was discrepant in relation to most previous studies, which indicate obesity as one of the risk factors for any types of cancers, including prostate cancer (FERNANDES *et al.*, 2014; BRASIL, 2015). Obesity represented one of the lowest rates compared to the eutrophic and malnourished, i.e., below the BMI described in the literature, as a risk factor for PC.

Supposedly, this result may be due to the regional profile of the hospital and the area of coverage that the institution reaches (regions of the state of Minas Gerais with low per capita income, low education,

underemployment, rural workers, and the like) and neighboring states (Rio de Janeiro, Espírito Santos, and Bahia), in which the patients have profiles identical to those of Minas Gerais.

Regarding the prevention of PC, the study shows that most patients underwent a PSA exam. However, this index raises doubts, because probably the numbers described in the stages (III, IV) of this neoplasm would not correspond to 52.4% of all patients. Therefore, we can see an incompatibility between prevention and installed disease. It is believed that this is due to the fact that patients arrive with symptoms of the diseases and, in basic health units, PSA exams are requested by the attending physician for propedeutics of complaints (obstruction, dysuria, hematuria, among others). The difficulty in *screening* for PC shows the lack of awareness of men about the need to perform periodic preventive examinations.

Regarding the Gleason value, the median found was 7 demonstrating intermediate risk of PC. Most are between low and intermediate risk, compatible with what is described by the National Cancer Institute (INCA), that is, that intermediate scores, between 5 and 7, can mean a slow or fast growing cancer and this growth will depend on a number of other factors, including the time during which the patient has the cancer (BRASIL, 2002/2015).

As for the staging, there was a small number of patients in stage I (35, 3.7%), which may reflect the regional population with low education and poor level of information that contributes to late diagnosis of the disease. Another important factor is the age of patients with prostate cancer, being primarily elderly. In stage II, the great majority presented initial disease, curable with surgical or radiotherapeutic procedures and, due to the advances in medical techniques and greater routine of screening tests such as PSA, justifies such an index. In advanced stages (III and IV) a considerable number of patients were already admitted to the hospital with incurable diseases, added to previous clinical conditions such as advanced age and previous comorbidities. As for the small percentage without information on staging compared to the other variables that present high percentages, it denotes the importance of a service with reliable follow-up records. The staging information is collected by the hospital's RHC.

The authorization of palliative hormone therapy at any stage may be valid, since it depends on the clinical conditions that the patient is in. When the tumor is inoperable, which justifies treatment with radiotherapy or hormone therapy or palliative therapeutic conducts (BRASIL, 2002/2014).

Among all the hormonal medications present in the pharmacological market and that are part of the therapeutic "arsenal" for HCM, the most widely used has been leuprorrelin acetate, an LHRH agonist administered subcutaneously. There are three dosages that are usually administered in HCM (7.5mg monthly, 22.5mg quarterly, and 45mg every six months).

Leuprorrelin acetate is a synthetic analog of the natural gonadotropin-releasing hormone (LHRH), acts as a potent inhibitor of pituitary gonadotropin secretion, and suppresses testicular and ovarian stereogenesis. Administration of LA results in an initial increase in circulating levels of LH and FSH, causing a temporary increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in men,

and estrone and estradiol in women) (HUGGINS *et al.*, 1941; PORCARO et *al.*, 2016; OHLMANN; GROSS-LANGENHOFF, 2018).

This study reported the largest Brazilian real-world analysis to date on the efficacy and safety of Eligard® deposition in men with PC, registered and treated at HCM-MG, Brazil. Since this was a retrospective observational study and with great difficulty in obtaining data from medical records, the final outcome was designed as baseline, 6 and 12 months after the beginning of Eligard® PSA dosages. As soon as the Eligard® formulation was launched, three non-interventional studies were published aiming to assess the efficacy, tolerability and/or impact on the quality of life of LHRH agonists in daily clinical practice: a French study, ELIRE (3- and 6-month formulations), (CHU *et al*, 2002) a Belgian MANTA (1 and 3 month formulations) (CRAWFORD *et al.*, 2006) and a German one (6 month formulation) (OUZAID; ROUPRET, 2011; OHLMANN; GROSS-LANGENHOFF, 2018).

When evaluating the data from the present study regarding monthly, quarterly, and semiannual Eligard® formulation, the results demonstrated substantial reduction (99.7%) of median PSA levels by the referred Eligard® depot formulations after treatment initiation. Clinical trials (OUZAID; ROUPRET, 2011; CRAWFORD *et al.*, 2006; MOTTET *et al.*, 2016; OHLMANN; GROSS, 2018) demonstrate the efficacy and tolerability of drugs in homogeneous patient populations that meet very specific inclusion and exclusion criteria. In this study, with a heterogeneous population, the ease of use and local tolerability of the Eligard® depot formulation were determinants for the indication of this medication and also corroborated by the oncology nursing team at HCM-MG, Brazil.

According to Ohlmann and Gross-Langenhoff (2018), real-world studies are larger and include many more patients in the populations seen in routine clinical practice, and compared to patients enrolled in clinical trials with Eligard® the patient population was more heterogeneous, with relative numbers of tumor stages, Gleason variations, indications for androgen deprivation, and comorbidities at the start of the study. Many of these patients would have been excluded from the clinical trials.

As there is great variability in the PSA data, the median was chosen as the best measure to represent it. OHLMANN and GROSS-LANGENHOFF (2018) also evaluated the median PSA due to the heterogeneity of the data. Our studies demonstrate that PSA levels can be effectively reduced in most of the broad population of patients treated with monthly, quarterly, and semesrtal Eligard® injections.

This is reflected in the upper end of the range of PSA values measured at the beginning of this study. The results showed that median serum PSA levels were reduced from 25.6 to 0.08 ng/mL, 12 months after the baseline visit for monthly Eligard®. Results were comparable for the monthly, quarterly and semi-annual Eligard® depot formulations, with reductions in median PSA levels from 28.8 to 0.09 ng/mL and from 23.2 to 0.04 ng/mL at 12 months after the baseline visit, respectively. All comparisons were statistically signficant. Comparing with the studies by OHLMANN and GROSS-LANGENHOFF (2018), CHU *et al.* (2002) and CRAWFORD *et al.* (2006) in which Eligard® posologies quarterly (5.3-31.0

ng/mL), semi-annually (0.1-2.4 ng/mL) and annually (0.1-1.9 ng/mL), (MOTTET *et al.*, 2011; MOTTET *et al.*, 2016) found similarity between the results obtained in the studies. In addition, it was noticed divergence of this study in relation to clinical trials, (OHLMANN; GROSS-LANGENHOFF, 2018; MOTTET *et al.*, 2011; MOTTET et *al.*, 2016), where considerable number of patients received Eligard® in combination with anti-androgen, bisphosphonate or chemotherapeutic agent, and in the present HCM study different from others already published, patients received only Eligard® at initiation of therapy (MOTTET *et al.*, 2011; MOTTET et *al.*, 2016).

Adverse events were reported less frequently in this study compared to clinical trials using the 3- and 6-month period of Eligard® (MOTTET *et al.*, 2011; MOTTET *et al.*, 2016). Serious adverse events (SAEs) occurred in less than 1% of patients, being cardiovascular adverse side effects: stroke (n=2), hemorrhagic stroke, coronary insufficiency, peripheral vascular insufficiency, angina, PTE and AMI (n = 1/each) being that they already had the underlying cardiovascular diseases and previous events (stroke, coronary insufficiency, AMI and angina). In analysis of the medical records, few patients had comorbidities associated, and almost always, with irregular use of medications to control chronic diseases (mainly metabolic syndromes). The previous comorbidities are very serious, and require strict control, which is not confirmed in the information contained in the medical records. These, associated with obesity, sedentary lifestyle, and low per capita income, impose on the patient the only alternative left to him, which is to seek medications provided by the municipal health clinics, where they are not always found and/or provided correctly. Thus, possibly the use of Eligard® could not be the causality of these EAG, representing less than 1% of the 932 patients analyzed, and of these, 85% have previous cardiovascular diseases surveyed.

No patient discontinued treatment prematurely due to the mentioned events, including general weakness, fatigue, sweating attacks, and local swelling after Eligard injection® (LA).

Possible explanations for this discrepancy may be for the following reasons: the co-administration of antiandrogens, which can decrease the incidence of hot flashes (MOROTE *et al.*, 2007; OHLMANN; GROSS-LANGENHOFF, 2018) in about one third of patients; the use of another hormone therapy in a subgroup of patients at the time of Eligard® initiation. In daily clinical practice physicians consider such complaints as "normal" reactions following the injection of LHRH agonists.

The local tolerability of Eligard® has been evaluated and the results were satisfactory for the majority of patients. Due to the non-interventional nature of the studies reported here, the data collected is not as comprehensive as that collected in randomized studies and rigorous controlled clinical trials. However, after analysis, a large population in routine clinical practice in Brazil suggests the best, real-life use of Eligard® (LA). The data demonstrated here provide valuable information on the use of Eligard® (LA) in clinical practice in Brazil.

However, there were limitations to this study. Initially, it was intended to create as complete a database as possible containing patient data from the physical and electronic medical records. However,

this study had significant limitations in several aspects. The first and perhaps most relevant was the lack of information about the patients (housing, employment/unemployment, treatment expenses, for example, diabetes mellitus, hypertension, family support, use of alcohol and/or drugs, smoking, family history, nutritional status, Gleason value), the initial PSA or 6 and 12 months after starting treatment, which were also exclusion criteria in this study. According to Gonçalves (2008), this information is essential and should be included in medical records "to consolidate and/or substantiate risk factors" (GONÇALVES, 2008).

In any organization, including large, medium and small healthcare institutions, should have a database containing as much information as possible about the patient, his or her past and family history. One of the greatest benefits of a database is to provide the user with an overview of collected information, which can be designed to manage large volumes of patients, as is the case with HCM.

Moreover, the importance of reliable information contributes to feed epidemiological and clinical databases in government agencies of the three spheres (federal, state and municipal), assisting in the implementation of actions in public health policies. In the health area, one of the great difficulties in data collection is the diversification of nomenclatures, terms, acronyms, classifications, which makes it difficult to standardize information (FERREIRA *et al.*, 2001).

This understanding is reinforced by studies that indicate that in most underdeveloped countries there is an incomplete and precarious structure of the health system in the underreporting regarding the incidence, treatments, complications and mortality (BUSATO JÚNIOR; ALMEIDA, 2015). Due to lack of this information, the sample of the present study was reduced from 1,890 to 932 analyzed medical records.

6 CONCLUSIONS

Epidemiological characteristics: average age of 75 years, non-white (black + brown), married, most with low education, retired, rural workers, depend on the support of the Health Secretariats of their municipalities, low per capita income, most with their own homes, are treated by SUS, non-smokers, non-drinkers, no family history; and clinics mostly with stages II and III, treated with radiotherapy, comorbidities cardiovascular diseases, and adverse events considered from the treatment itself. Efficacy of the hormone (Eligard®): more than 99% drop in initial PSA after treatment with Eligard® in 6 and 12 months with good results. Patient tolerability of this medication, with very satisfactory results (very low rates of non-serious and serious adverse events).

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