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Active Surveillance for Prostate Cancer as treatment modality: experience at Basurto University Hospital

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Abstract

Introduction: Prostate cancer is the second most frequent cancer and the fifth leading cause of cancer death in men worldwide. Different treatment modalities are available for low-risk localized PC, one of them being Active Surveillance, which is defined as a monitoring strategy for patients with prostate cancer with the aim of deferring curative treatment. Several protocols have been proposed.

Materials and methods: This study includes all patients diagnosed with PC that have undergone or currently undergo AS as treatment modality at Basurto University Hospital between September 2014 and March 2019. Once a database was designed and data was collected, descriptive and comparative (variables related to progression) analyses were performed.

Results: These variables were not related to PC progression: age at diagnosis, BMI, ECOG, PC family history, alpha-blockers, statins, total PSA, PSA density, F/T PSA, clinical stage, number of previous biopsies, percentage of positive cylinders, larger length affecting a cylinder, HGPIN, ASAP, IIEF score. CCI score (a higher score was seen on patients that had progressed) was related to progression, and lose of QOL after RRP (measured using IIEF) was proved.

Conclusions: A strict selection of patients should be done when considering AS as a treatment option, specially focusing on the estimated 10-year survival. Additionally, the deferral of active treatment can be justified by seeing the results obtained regarding QOL deterioration after RRP. The results of this study should be further studied by extending this study and including more patients into it. Furthermore, longer follow-up is needed in order to know oncological outcomes.

Keywords: Prostate Cancer, Active Surveillance, Progression, Quality of Life

LIST OF ABBREVIATIONS

AS: Active Surveillance

ASAP: Atypical Small Acinar Proliferation

BMI: Body Mass Index

BPH: Benign Prostatic Hyperplasia

CCI: Charlson Comorbidity Index

CSS: Cancer Specific Survival

DRE: Digital Rectal Examination

EAU: European Association of Urology

ECOG: Eastern Cooperative Oncology Group

ED: Erectile Dysfunction

F/T PSA: Free PSA / Total PSA

GS: Gleason Score

IIEF: International Index of Erectile Function

IPSS: International Prostate Symptom Score

ISUP: International Society of Urological Pathology

mpMRI: Multiparametric Magnetic Resonance Imaging

OS: Overall Survival

PC: Prostate Cancer

PIN: Prostatic Intraepithelial Neoplasia

PIRADS: Prostate Imaging Reporting and Data System

PSA: Prostate Specific Antigen

QOL: Quality of Life

RP: Radical Prostatectomy

RRP: Robotic Radical Prostatectomy

TNM: Tumor Node Metastasis

TP: Transperineal

TR: Transrectal

TRUS: Transrectal Ultrasound

US: Ultrasound

WHO: World Health Organization

WW: Watchful Waiting

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1. INTRODUCTION

1.1. PREVALENCE OF PROSTATE CANCER

According to statistics estimated by the International Agency for Research on Cancer in 2018 prostate cancer (PC) is the second most frequent cancer and the fifth leading cause of cancer death in men worldwide (excluding non-melanoma skin cancers). Additionally, as shown in **Figure 1** PC is the most frequent diagnosed cancer among men in more than half of the countries in the world, and the leading cause of cancer death among men in 46 countries[1].

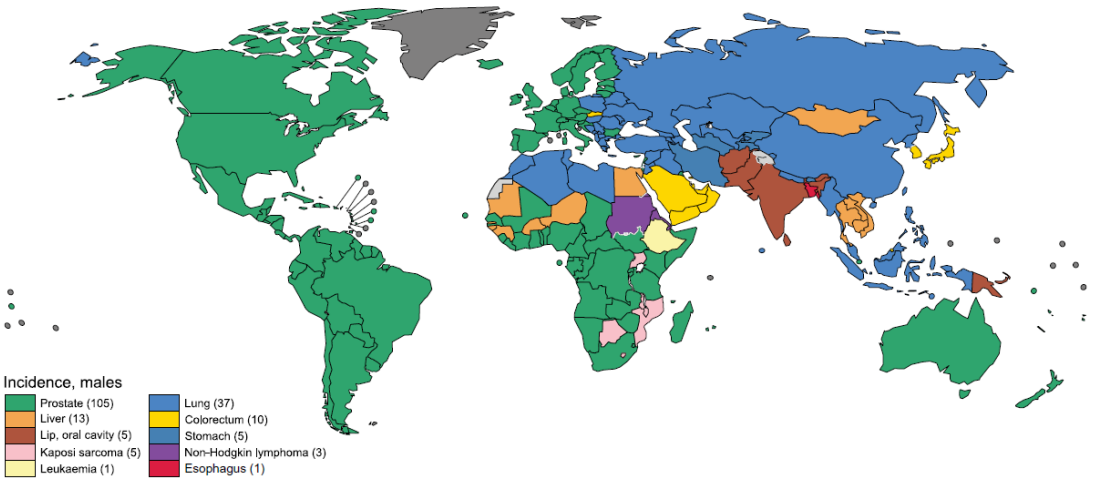


Figure 1. Global map presenting the most common type of cancer incidence in 2018 in each country among men. The numbers of countries represented in each ranking group are included in the legend. Source: GLOBOCAN 2018.

Regarding Europe, PC is the most frequent cancer among men and the third overall. The highest rates are found in Northern and Western Europe (1st Ireland with 189.3 cases per 100,000 inhabitants, 2nd Estonia and 3rd Norway) and the lowest in Central and Eastern Europe (40th Albania with 37.0 cases per 100,000 inhabitants, 39th Romania and 38th Ukraine). The average incidence in Europe is 100.9 cases per 100,000 inhabitants and the average in EU-28 countries is 113.6[2].

In Spain the average incidence as 2018 is 101.2 new cases per 100,000 inhabitants, lower than the EU-28 incidence. Moreover, it should be pointed out that Spain is the

second country with the lowest mortality rate in Europe (13.2 cases per 100,000 inhabitants)[2].

1.2. ETIOLOGY

As stated in the European Association of Urology (EAU) Guidelines, Hereditary Prostate Cancer is defined as the presence of three or more affected relatives, or at least two relatives who have developed early onset PC (< 55 years). Thus, approximately 9% of the diagnosed PCs are caused by patterns of inheritance[3].

Furthermore, several genetic studies have been carried out in order to determine the genetics related to PC. In addition to genetic factors, lifestyle and external factors may also be the cause of the development of PC in an individual. See **ANNEX 1** for deeper research upon these matters.

1.3. SCREENING AND DIAGNOSIS

The World Health Organization (WHO) defines screening as *"the presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests, examinations or other procedures that can be applied rapidly and easily to the target population"*[4].

Nowadays, there is a great discussion about the implementation of screening for PC, with diverse opinions among several international organizations. Different recommendations regarding PC screening have been included in **ANNEX 2**.

1.3.1. Prostate biomarkers

Although there is no specific marker for PC there are several markers that might direct towards the diagnosis of PC. The most known marker is the Prostate Specific Antigen (PSA), which is organ but not cancer specific. Thus, elevated levels can be found in Benign Prostatic Hyperplasia (BPH), prostatitis and other non-malignant conditions[5]. A PSA level of more than 4.0 ng/ml was considered to have predictive value for PC[6]. However, an important number of cases were missed and, therefore, other markers are being used:

- PSA density: It is the level of serum PSA divided by the transrectal ultrasound determined prostate volume and is a strong predictor of adverse pathological features and biochemical recurrence after radical treatment[7,8].
- Free PSA / Total PSA: In patients with a total PSA value of 2.1 to 4 ng/ml using 0.15 as the cut-off point of Free PSA/Total PSA (F/T PSA), cancer is detected more frequently[8]. Contrarily, in patients with a PSA value between 4 and 10 ng/ml the use of F/T PSA is controversial. Some argue favorably to its use as a value of <0.1 results in a 56% positive biopsy[3]. Others argue that the F/T PSA determination has a low sensitivity and specificity for the diagnosis of PC in men with PSA values 4-10 ng/ml[9]. F/T PSA is of no clinical use if the total serum PSA is > 10 ng/mL or during follow-up of known PC[3].
- PSA velocity: Absolute annual increase in serum PSA (ng/mL/year). A higher PSA velocity count was related to a higher risk and more aggressive PC[10], although nowadays the EAU advocates that this marker does not provide additional information compared to the total PSA alone[11].
- PSA doubling time: It measures the exponential increase in serum PSA over time. It has a prognostic value on PC, which is inversely correlated with the rate of prostate cancer dissemination and Gleason Score[12]. However, the EAU advocates that this marker does not provide additional information compared to the total PSA alone[11].
- PCA3: While this urine-based biomarker is expressed in androgen receptor positive PC cells, it is expressed at very low levels in the non-tumoral tissue and BPH cells. It is mostly used to determine the necessity of a new biopsy after an initially negative biopsy[13].
- 4k test: It is based on four kallikrein blood markers: total PSA, free PSA, intact PSA and the human kallikrein-related peptide 2. It is a valuable diagnostic and prognostic test for the management of early PC as it reduces the number of biopsies and it is linked to the aggressiveness of PC[14].
- Prostate Health Index: It is obtained by measuring free PSA, total PSA and kallikrein-like peptidase 2. It is also used to reduce the amount of unnecessary biopsies[15].

It should be emphasized that while some of the markers explained above are used for diagnosis, others can also be used during follow-up in certain treatment modalities.

1.3.2. Digital Rectal Examination

As a primary screening test, there is no evidence that Digital Rectal Examination (DRE) is beneficial, but DRE in men referred for an elevated PSA might be a useful secondary test[16]. Thus, most of the current Guidelines recommend the DRE + PSA as routine screening when indicated. According to the EAU Guidelines a suspect DRE in patients with a PSA level ≤ 2 ng/mL has a positive predictive value of 5-30% and a suspicious DRE is related to an increased risk of higher Gleason Score (GS), being that an indication for biopsy[3].

1.3.3. Imaging

Multiparametric magnetic resonance imaging (mpMRI) is currently booming. Hence, its use on diagnosis, biopsy and follow-up is being investigated. An international collaboration of the American College of Radiology, European Society of Uroradiology and AdMetech Foundation led to the development of the second version of Prostate Imaging Reporting and Data System (PIRADS v2)[17]. Its main goal is to promote global standardization and reduce variability in the acquisition, interpretation, and reporting of prostate mpMRI.

The PI-RADS v2 assessment categories are defined with the following scores[17]:

- 1: Very low (clinically significant PC is highly unlikely to be present)
- 2: Low (clinically significant PC is unlikely to be present)
- 3: Intermediate (the presence of clinically PC disease is equivocal)
- 4: High (clinically significant PC is likely to be present)
- 5: Very high (clinically significant PC is highly likely to be present)

1.3.4. Prostate-biopsy

In terms of prostate-biopsy, ultrasound-guided biopsy is the standard. According to the EAU guidelines, it is recommended to obtain at least 8 cylinders in prostates with a size of about 30 cc. If the size is larger 10-12 cylinders is recommended with more than twelve cores not being significantly more conclusive[3].

There are two main approaches to obtain prostate-biopsies: transrectal (TR) and transperineal (TP). In the TR biopsy, the needle punctures through the anterior rectal wall guided by the ultrasound (US). But in TP biopsy, the needle punctures through the skin of perineum. No significant differences are found in terms of efficiency and complications between TP and TR approaches for prostatic biopsy. However, in terms of pain relief and additional anesthesia, TR biopsy has better outcomes[18].

There are different imaging techniques to obtain the biopsies[19]:

- TRUS guided biopsy: the prostate is visualized by using a TRUS and biopsies are taken while the prostate is being watched.
- Cognitive targeted biopsy: mpMRI is done prior to the biopsy and the prostate is visualized by using a TRUS. If a suspicious zone is observed through mpMRI a targeted biopsy of that suspicious zone is taken together with biopsies from the rest of the prostate.
- mpMRI/TRUS fusion software-based targeted biopsies: If a suspicious image is seen, that image is fused with the image obtained through the TRUS. Thus, the suspicious image can be seen on the US even if it is not suspicious just using the US.

Major complications are rare when obtaining prostate biopsies, being hematospermia, hematuria and rectal bleeding the most common ones[3].

In addition to PC, two major findings can be observed on a biopsy:

- Atypical Small Acinar Proliferation (ASAP): It is an indication to repeat the biopsy as there is a 31-40% PC risk in the following biopsy[20, 21].
- Prostatic Intraepithelial Neoplasia (PIN): It is an indication to repeat the biopsy as there is around 30% PC risk in the following biopsy[21, 22].
- ASAP + PIN: it is an indication to repeat the biopsy as there is around 50% PC risk on the following biopsy[23].

1.4. CLASSIFICATION AND STAGING

1.4.1. Clinical Tumour Node Metastasis (TNM) classification

Clinical T stage only refers to DRE findings; imaging findings are not considered in the TNM classification. Pathological staging (pTNM) is based on histopathological findings and is quite similar to the clinical TNM, except for clinical stage T1c and the T2 substages. All histopathologically confirmed organ-confined PCs after radical prostatectomy are considered pathological stage T2 and the Union for International Cancer Control does not recognise pT2 substages anymore[24]. (See: **Table 1**)

Table 1. Clinical Tumor Node Metastasis (TNM) classification of Prostate Cancer 8th edition.

T – Primary Tumor (stage based on DRE only)
TX Primary tumor cannot be assessed
T0 No Evidence of primary tumor
T1 Clinically unapparent tumor that is not palpable
T1a Tumor incidental histological finding in 5% or less of tissue resected
T1b Tumor incidental histological finding in more than 5% of tissue resected
T1c Tumor identified by needle biopsy (e.g. because of elevated PSA)
T2 Tumor that is palpable and confined within prostate
T2a Tumor involves one half of one lobe or less
T2b Tumor involves more than half of one lobe, but not both lobes
T2c Tumor involves both lobes
T3 Tumor extends through the prostatic capsule
T3a Extracapsular extension (unilateral or bilateral)
T3b Tumor invades seminal vesicle(s)
T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N – Regional (pelvic) Lymph Nodes (Metastasis no larger than 0.2 cm can be designated pNmi)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
M – Distant Metastasis (When more than one site of metastasis is present, the most advanced category is used)
M0 No distant metastasis
M1 Distant metastasis
M1a Non-regional lymph node(s)
M1b Bone(s)
M1c Other site(s)

1.4.2. Gleason Score and International Society of Urological Pathology 2014 grade

In 2005, the International Society of Urological Pathology (ISUP) modified the GS as follows: Gleason grade of the most extensive pattern plus the second most common pattern (when two patterns are present). If only one pattern is present it must be doubled. In 2014, the ISUP Gleason Grading Conference of Prostatic Carcinoma was held and a decision to limit the number of PC grades, ranging them from 1 to 5, was made. (See: **Table 2**)

Table 2. Gleason Score and the equivalent International Society of Urological Pathology 2014 grades.

Gleason Score	ISUP Grade
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4 or 3+5 or 5+3)	4
9-10	5

1.4.3. EAU risk group classification

The EAU risk group classification is based on the grouping of patients with a similar risk of biochemical recurrence after radical prostatectomy or external beam radiotherapy, based on D'Amico's classification system for PC[25]. (See: **Table 3)**

Table 3. EAU risk group classification

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

1.5. LOCALIZED LOW-RISK PROSTATE CANCER TREATMENT

Different treatment modalities are available for low-risk localized PC: Active Surveillance (AS), Radical Prostatectomy and Radiation Therapy. Besides, Watchful Waiting (WW) can be used as palliative treatment in a first-line setting in both localized and locally-advanced PC[3, 16].

Several studies have been performed with long-term survival on patients diagnosed with low-grade PC as a matter of study[26, 27, 28]. Thus, it was concluded that in patients with low-grade PC mortality from PC was as low as 7% after fifteen years follow-up[26].

1.5.1. Watchful waiting

It was seen that in patients with an estimated less than 10-year survival score, 90% of men died from competing causes and that tumour aggressiveness had little impact on survival. Thereby, the use of WW, which is defined as *"the management of patients with a limited life expectancy, in whom palliative treatment (without curative intent) is initiated if symptoms develop"*[29], was justified[30].

The estimated 10-year survival score is mainly calculated using the Charlson Comorbidity Index (CCI) Score[31, 32, 33]. It is a method of predicting mortality by classifying or weighting comorbid conditions. See **ANNEX 3** to consult variables and their punctuations, as well as the formula.

Patients' functional status should be also taken into account when the decision to use a deferred treatment is made; in fact, several methods can be used to measure the functional status being the Eastern Cooperative Oncology Group (ECOG) Performance Status widely used[34].

1.5.2. Active surveillance

Several studies have analyzed the Overall Survival (OS) and Cancer Specific Survival (CSS) in patients that have followed different Active Surveillance strategies. It can undoubtedly be said that both OS and CSS are extremely good, reaching a 10-year OS of up to 98% and CSS of up to 100%[35-42]. Taking into account these results a new treatment modality known as Active Surveillance started to be

introduced as treatment for localized low-risk PC. AS is defined as *"a monitoring strategy for patients with prostate cancer with the aim of avoiding or deferring curative treatment"*[29]. As it has been said before, due to the indolent nature of low-risk tumors, AS is an appealing alternative and can avoid or allow the postponement of radical treatments.

1.5.2.1. Selection criteria for AS

The relative novelty of AS and the lack of studies that compare different selection criteria means that there is no international consensus regarding the selection criteria that should be considered when including a patient into an AS protocol. The criteria most often published include: ISUP grade 1; when specified, < 2-3 positive cylinders with < 50% cancer involvement in every positive cylinder; a clinical T1c or T2a; a PSA < 10 ng/mL and a PSA density < 0.15 ng/ml/cc[43, 44].

Three AS protocols of major importance have been chosen and included in **Table 5.**

Table 5. Characteristics of active surveillance selection criteria of various protocols

AS protocol	Clinical stage	PSA (ng/ml)	Gleason score	No. of positive cylinders	% Cylinder involvement
PRIAS[45]	≤T2	≤10	≤6	≤2	-
Royal Marsden[46]	≤T2a	≤15	≤6 (Gleason 3 + 4 if over 65 years)	≤50%	-
Sunnybrook[47]	-		≤6 (aGleason 3 + 4 if favorable risk (PSA 10–20))	≤2	≤50%

1.5.2.2. Confirmatory biopsy

Additionally, numerous studies have suggested, and it is widely accepted and applied, the need for a confirmatory biopsy six to twelve months after the first positive biopsy in order to confirm the grade seen in the first biopsy[48, 49]. Three clinic-pathological variables were significantly associated with reclassification: PSA-density, > 2 positive cores, and African-American race[50].

1.5.2.3. Follow-up

The follow-up strategy is based on serial DRE at least once yearly, PSA at least once every six months and repeated biopsy at a minimum interval of three to five years

according to the EUA guidelines[3]. Most major AS protocols follow a similar strategy with clinical follow-up, DRE, and PSA testing every 3–6 months.

The same three AS protocols can be seen in **Table 6.**

Table 6. Follow-up strategies for active surveillance of various protocols

AS protocol	DRE	PSA	Confirmatory biopsy	Subsequent biopsy
PRIAS[45]	-	3 months for 2 years; 6 months subsequently	At 1 year	At 4 and 7 years
Royal Marsden[46]	3 months for 1st year; 4 months for 2nd year; 6 months subsequently	Monthly in year 1, every 3 months in year 2, then every 6 months	-	At 18–24 months
Sunnybrook[47]	3 months for 2 years; 6 months subsequently	3 months for 2 years; 6 months subsequently	<1 year	Every 3 to 4 years until 80 years of age

It is remarkable that it has been stated that there are some independent predictors of upgrading after a 3-years follow-up: ISUP grade 2, PSA density > 0.15 ng/mL/cm3 and a PIRADS 5 lesion on MRI[51].

1.5.2.4. Quality of Life

One of the main reasons to use AS is the improvement in the Quality of Life (QOL). In fact, if active treatment is postponed, all the side effects that active treatments bring with them are postponed too.

QOL is usually measured using several tools. Most commonly, questionnaires are used: (See **ANNEX 4**)

- International Prostate Symptom Score (IPSS): It is based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life.
- International Index of Erectile Function (IIEF): Used to evaluate erectile function.
- CAVIPRES (named after Spanish “Cuestionario Español de Calidad de Vida en Pacientes con Cáncer de Próstata”): gathers information regarding social and partner support, psychological conditions of the patients, and also life

expectancies against disease outcome together with classical prostatic symptomatic parameters.

Compared to other active treatments, AS has shown a better QOL in all aspects except for anxiety, as patients in which AS is decided show a higher incidence of anxiety[52, 53]. Compared to RP, after a 3-year follow-up patients who had undergone RP had significantly poorer urinary, sexual function and sexual bother scores[54]. Other authors published that after a 24-month follow-up QOL between those who had been treated and those on AS was similar[55].

1.5.2.5. Switching to active treatment

Here again, there is no international consensus regarding when a patient should switch to active treatment. Most of the protocols say that active treatment should be considered when there is a change in the biopsy results (ISUP grade, number of positive cylinder, cylinder length involvement), or T-stage progression.

Two AS protocols have been included in **Table 7.**

Table 7. Clinical and pathologic indications for active treatment consideration

AS protocol	Gleason score	No. Of positive cylinders	% Cylinder involvement	PSA doubling time (years)	PSA velocity
PRIAS[45]	>6	>2	-	<3	-
Royal Marsden[46]	≥4 + 3	>50% of cylinders	-	-	>1 ng/ml

1.5.2.6. Role of mpMRI in AS

As it has been explained before, 6 to 12 months after the diagnostic biopsy a confirmatory biopsy is usually taken. When mpMRI/TRUS fusion software-based targeted biopsies are taken, an additional 27% of tumors are upgraded. Using TRUS guided biopsies and mpMRI guided biopsies on their own 17% of the patients are missed. Thus, combining the two biopsy techniques would be the best way to select patients for AS at confirmatory biopsy[56].

The use of mpMRI during follow-up is still controversial. It is clear that a positive mpMRI is a positive predictor for upgrading as upgrading is detected in positive mpMRI three times more often than in negative mpMRI[57]. However, there is not enough data to say that a patient with a negative mpMRI should not undergo a follow-up biopsy[58].

1.5.3. Watchful waiting compared with active surveillance

Therefore, active surveillance and watchful waiting are both deferred treatment modalities. On the one hand, AS's objective is to avoid overtreatment in men with localized PC who do not require immediate treatment, but at the same time achieve the correct timing for curative treatment in those who eventually do require to be treated. Patients undergo an exhaustive follow-up and curative treatment is decided when the tumor progresses but it is still curable. On the other hand, WW is applied on patients that are taken as incurable (not only because of PC stage but also due to expected low survival as a result of comorbidities) from the diagnosis of PC and palliative treatment is applied when symptoms related to PC are developed.

Table 4 summarizes the main differences between both strategies[26].

Table 4. Differences between Active Surveillance and Watchful Waiting. Source: EAU

	Active Surveillance	**Watchful Waiting**
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient-specific
Assessment / markers used	DRE, PSA, re-biopsy, mpMRI	Not predefined
Life expectancy	< 10 years	<10 years
Aim	Minimize treatment-related toxicity without compromising survival	Minimize treatment-related toxicity
Comments	Low-risk patients	Can apply to patients with all stages

2. OBJECTIVES

- To conduct an epidemiological, clinical and anatomopathological descriptive study on patients who follow the AS protocol in Basurto University Hospital and evaluate its compliance.
- To perform a comparative study in order to identify variables related to PC progression in patients undergoing AS.
- To analyze QOL regarding erectile function during follow-up and after active treatment with RRP; and to compare clinical and pathologic results before and after RRP.

3. MATERIALS AND METHODS

This study includes all patients diagnosed with PC that have undergone or currently undergo AS as treatment modality at Basurto University Hospital between the 3rd September 2014 and the 8th March 2019.

3.1. BASURTO UNIVERSITY HOSPITAL AS PROTOCOL

Some of the patients included in this study underwent AS but did not follow any specific protocol until 2017, when a protocol was introduced.

The followed AS protocol has the following **inclusion criteria**:

- Gleason 6
- ≤2 positive cylinders with <50% of tumor in each positive cylinder
- Clinical T1c or T2a stage
- PSA <10 ng/ml and PSA density <0.15 ng/ml/cc
- Life expectancy >10 years

Aside from meeting the inclusive criteria, patients must not meet any of the **exclusion criteria**:

- Prevailing ductal carcinoma (including pure intraductal carcinoma)
- Sarcomatoid carcinoma
- Small-cell carcinoma

Follow-up is also set in the AS protocol:

- Digital rectal examination: once a year
- PSA: every 6 months
- Confirmation biopsy 6 months after 1st positive biopsy with previous mpMRI (if mpMRI localizes PI-RADS 3/4/5 areas: mpMRI/TRUS fusion software-based targeted biopsy)
- Biopsy at least every 3 years or when clinically indicated (PSA, DRE)

The decision to proceed to **active treatment** is made whenever any of the following facts are detected:

- Biopsy changes:
  - Increasing Gleason Score
  - Increasing number of positive cylinders
- Stage (only taking into account T) progression
- Increasing PSA (specially PSA Doubling Time < 3 years)
- Patient's request

3.2. SELECTION OF VARIABLES FOR DATABSE

Once the objectives were established the next step was to build a database regarding the different aspects of the PC cases that follow the AS protocol at Basurto University Hospital. The selection of variables was inspired by a number of databases provided by the Urology service whose study of matter was PC. Furthermore, the Research Platform for Multicenter Studies used by the Spanish Urological Association (AEU-PIEM in Spanish) was also checked.

The final selection of variables agreed was as follows:

- Patient's general data:
  - Date of birth
  - Age at PC diagnosis
  - Race
  - Living area
  - Education level
  - Marital status
  - Employment status
  - Physical activity habits
  - Weight
  - Height
  - Body Mass Index (BMI)
  - ECOG score

  - Charlson score
- Clinical data when PC was diagnosed:
  - PC family history
  - Prostate -argeted medical treatment and statins
  - Prostate surgical treatment before diagnosis
  - Staging methods and results
  - Number of biopsies prior to diagnosis
  - Free PSA
  - Free PSA / Total PSA
  - PSA density
- Clinical and anatomopathological data when PC was diagnosed and during follow-up:
  - Date
  - Total PSA
  - Clinical stage
  - Quality of life questionnaires
  - Prostate US volume
  - Biopsy: number of obtained cylinders, number of positive cylinders, percentage of positive cylinders, Gleason score, larger length affecting a cylinder, perineural invasion, PIN presence, ASAP presence, biopsy technique
  - Pathologic, local or metastatic progression
- Follow-up time until active treatment, reason, number of follow-ups before treatment, decided treatment.

3.3. ETHICS AND INVESTIGATION COMMITEE

After the selection of variables was agreed, an application was written to Basurto University Hospital's Ethics and Investigation Committee in order to obtain the approval to conduct the study and gain access to their medical records.

3.4. PATIENT SELECTION

Once the approval was obtained (See **ANNEX 5**) a list of 70 patients was provided by this study's director and the data collection began. After setting up the structure of the database, an individual, case by case, review of the medical records of the patients was carried out in order to complete it.

A total of 17 patients were not included in this study after reading their medical records:

- There was no access to 2 patients' medical record
- A woman was mistakenly included
- 4 patients had received treatment for PC but never followed the AS protocol as they were treated when PC was diagnosed
- 2 patients were diagnosed with PC and followed AS in a private institution but afterward treated in Basurto University Hospital. A lack of data from the diagnosis and follow-up carried out in a private hospital out of Basurto University Hospital was detected
- 8 patients were diagnosed with PC as a result of having received treatment for BPH with transurethral resection

Thus, a total of 53 cases have been included into the database. The first PC diagnosis included in this study was on the 3rd September 2014 and the last included follow-up was on the 8th March 2019. Hence, this study encompasses all patients that have followed the AS protocol between those dates.

3.5. CODIFICATION OF THE VARIABLES

After selecting the variables, most of the qualitative ones were codified into numbers, in order to be able to collect data in a way that would allow a posterior statistical analysis. Some variables were not codified as their characteristics made them unsuitable for statistical analysis (i.e. date of birth, diagnose date, follow-up date, reason for active treatment, decided treatment).

Age at diagnosis (collected in years), weight (collected in Kg), height (collected in cm), BMI (collected in kg/m^2), number of biopsies prior to diagnosis, free PSA

(collected in ng/ml), total PSA (collected in ng/ml), free PSA/total PSA (collected in %), PSA density (collected in ng/ml/cc), prostate US volume (collected in cc), number of obtained cylinders, number of positive cylinders, percentage of positive cylinders (collected in %), larger length affecting a cylinder (collected in mm), follow-up time until active treatment (collected in months) and number of follow-ups before treatment were used in the statistical analysis, but, as they are quantitative variables, there was no need to codify them.

Four of the mentioned variables were obtained as the result of other variables:

- BMI: mass (kg) / height^2 (m)
- PSA density: total PSA (ng/ml)/ prostate volume (cc)
- Free PSA (ng/ml) / Total PSA (ng/ml)
- Percentage of positive cylinders: (number of positive cylinders / number of obtained cylinders) * 100

3.5.1. Race

White patients were assigned a 1, black patients a 2, Asian men a 3 and Maghrebi men a 4.

3.5.2. Living area

Patients that lived in the city were assigned a 1 and patients that lived in the countryside a 2.

3.5.3. Education level

Patients with no studies were assigned a 1, patients that had completed elementary education were assigned a 2, patients that had completed intermediate education were assigned a 3 and patients that had completed high education were assigned a 4.

3.5.4. Marital status

Patients that had a partner when diagnosed were assigned a 1, patients that had no partner were assigned a 2 and patients that had widowed were assigned a 3.

3.5.5. Employment status

Patients that were working when diagnosed were assigned a 1, those that were retired were assigned a 2, those that were unable to work were assigned a 3 and those that were unemployed were assigned a 4.

3.5.6. Physical activity

Patients that did not do any physical activity when diagnosed were assigned a 1, those who did it occasionally were assigned a 2 and those who did it regularly were assigned a 3.

3.5.7. ECOG Score

ECOG score was obtained based on the ECOG Performance Status classification following the guidelines of the Eastern Cooperative Oncology Group, thus distributing the patients into ECOG 0, 1, 2, 3 and 4. The variable was codified by assigning the corresponding number to the ECOG Score (0 to 4). ECOG 5 was not included as it is the punctuation given to those who are dead. (See: **Table 8**)

Table 8. ECOG Performance Status. Source: Eastern Cooperative Oncology Group.

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

3.5.8. Charlson Comorbidity Index Score

Charlson Comorbidity Index Score was calculated by using "MD Aware, LLC. (2018). MDCalc Medical Calculator (Version 1.0.22) [Mobile application software]. Retrieved from https://play.google.com/store". The variable was codified by assigning the corresponding number to the CCI Score. (See: **Table 9**)

Table 9. Charlson Comorbidity Index Score and estimated 10-year survival. Source: own elaboration.

CCI SCORE	ESTIMATED 10-YEAR SURVIVAL
0	98%
1	96%
2	90%
3	77%
4	53%
5	21%
6	2%
≥7	0%

3.5.9. PC family history

Patients with no PC family history were assigned a 0 and those with family history were assigned a 1. Additionally, 3 sub-variables were created for those that did have PC family history: first, second and third degree family members. Again, 0 and 1 were used in each of the sub-variables to specify the family member that had had PC.

3.5.10. Medical treatment

Patients that did not take any medication when diagnosed were assigned a 0 and those who did were assigned a 1. Additionally, 3 sub-variables were created for those who did take medication: alpha-blockers, 5-alpha-reductase inhibitors and statins. Again, 0 and 1 were used in each of the sub-variables to specify if they did not take that treatment (0) or they did (1).

3.5.11. Prostate surgical treatment before diagnosis

Patients that had not received any surgical treatment before diagnosis were assigned a 0 and those who did, were assigned a 1. Additionally, 2 sub-variables were created for those who did receive surgical treatment before diagnosis: transurethral resection of the prostate and prostatic adenomectomy. Again, 0 and 1 were used in each of the sub-variables to specify the surgical treatment they had received.

3.5.12. Staging methods and results

Patients that were not staged using TRUS were assigned a 0 and those who were staged using TRUS were assigned a 1.

Patients that were not staged using abdominal US were assigned a 0 and those who were staged using abdominal US were assigned a 1.

Patients that were not staged using CT scan were assigned a 0 and those who were staged using CT scan were assigned a 1.

Patients that were not staged using mpMRI were assigned a 0 and those who were staged using mpMRI were assigned a 1. Additionally, a sub-variable was created to obtain the mpMRI result when it had been done: a non-suspicious result was assigned a 0, PIRADS 1 result was assigned a 1, PIRADS 2 result was assigned a 2, PIRADS 3 result was assigned a 3, PIRADS 4 result was assigned a 4, PIRADS 5 result was assigned a 5 and a suspicious result (not categorized using PIRADS) was assigned a 6.

3.5.13. Clinical stage

Patients with cT1a stage were assigned a 1, those with cT1b stage were assigned a 2, those with cT1c stage were assigned a 3, those with cT2a stage were assigned a 4, those with cT2b stage were assigned a 5, those with cT2c stage were assigned a 6 and those with cT3a stage were assigned a 7.

3.5.14. Quality of life questionnaires

Patients that had not completed IPSS questionnaire were assigned a 0 and those that did were assigned a 1. Additionally, 2 sub-variables were created for those who did complete it and the scores were collected as quantitative variables: questions 1-7 and question 8.

Patients that had not completed CAVIPRES questionnaire were assigned a 0 and those that did were assigned a 1. Additionally, a sub-variable was created where the addition of all questions was collected.

Patients that had not completed IIEF questionnaire were assigned a 0 and those that did were assigned a 1. Additionally, a sub-variable was created where the addition of all questions was collected.

3.5.15. Gleason score

Three sub-variables were created: the first two corresponded with each of Gleason score's and the third corresponded to the addition of both numbers.

3.5.16. Perineural invasion

Patients with no perineural invasion were assigned a 0 and those with perineural invasion were assigned a 1.

3.5.17. HGPIN presence

Patients with no HGPIN presence were assigned a 0, those with HGPIN in diagnose biopsy were assigned a 1, those with HGPIN in previous biopsies were assigned a 2 and those with HGPIN in diagnose and previous biopsies were assigned a 3.

3.5.18. ASAP presence

Those with no ASAP presence were assigned a 0 and those with ASAP presence were assigned a 1.

3.5.19. Biopsy technique

Patients that had their diagnose-biopsy obtained using only TRUS were assigned a 1, biopsies that were obtained using cognitive targeted biopsy technique were assigned a 2, those obtained using MRI/TRUS fusion software-based targeted biopsy technique were assigned a 3.

3.5.20. Pathologic progression

Pathological progression was considered when any of the following happened:

- Increasing Gleason score:
    - From 3+3 to ≥ 3+4

  - From 3+4 to ≥ 4+3
- Increasing tumor volume:
  - If follow-up biopsy is TR (total number of cylinders ≤20): >2 positive cylinders
  - If follow-up biopsy is TP (total number of cylinders 20-32): ≥3 positive cylinders and >2 affected zones
  - >5 millimetres or >50% of tumor in any cylinder (if the cylinder is >1 centimeter long)

Those patients with no pathologic progression were assigned a 0 and those with pathological progression were assigned a 1.

3.5.21. Local progression

Local progression was considered when the following happened:

- Change on staging: from cT1-cT2 to ≥ cT3a, detected by DRE or mpMRI.

Those patients with no local progression were assigned a 0 and those with local progression were assigned a 1.

3.5.22. Metastatic progression

Metastatic progression was considered when a positive N or M was found. Those patients with no metastatic progression were assigned a 0 and those with metastatic progression were assigned a 1.

3.6. STATISTICAL ANALYSIS

After completing the database, the following step was to perform the statistical analysis of the variables. The statistical analysis was performed using the IBM® SPSS® Statistics system.

3.6.1. Variable grouping

In order to perform the statistical analysis several variables were grouped using the IBM® SPSS® Statistics system as follows:

- Age at PC diagnosis: ≤55; 56-64; ≥65

- BMI: <25, [25-30), ≥30
- Charlson score: 0-6; ≥7
- Total PSA: ≤5; (5-10], >10
- PSA density: <0.15; ≥0.15
- Free PSA / Total PSA: <10; [10-20); ≥20
- Percentage of positive cylinders: ≤10; (10-20]; >20
- Larger length affecting a cylinder: ≤1; >1
- IPSS questionnaire:
    - 1-7 questions: 0-7; 8-19; 20-35
    - Question 8: 0-2; 3-6
- CAVIPRES questionnaire: 30-54; 55-78; 79-102; 103-126; 127-150
- IIEF questionnaire: <5; 6-10; 11-16; 17-25; 25-30

Race, living area, education level, marital status, employment status and physical activity habits variables were not used to perform the statistical analysis as almost not data was found during the review of the medical records.

3.6.2. Descriptive analysis

As the author of this study had no previous knowledge about the use of the mentioned system, "*IBM SPSS Statistics 25 Brief Guide"* was consulted and the basic descriptive operations of the system were learnt and executed by the author of this study.

3.6.3. Comparative analysis

In order to perform the comparative analysis, the consultation of the mentioned guide was not enough. Hence, the department of statistics at Basurto University Hospital was consulted in order to get information about the use of different statistical tests. Once the information was obtained the author of this paper performed the tests as follows:

- Comparison between qualitative variables: Pearson's chi-squared or Fisher exact tests were used.

- Comparison between 2 qualitative variables (when a qualitative variable had only 2 possibilities, e.g. PC family history: yes/no) and ≥1 quantitative variable(s): Student's t-test was used. As the sample used in this study is small, non-parametric tests needed to be performed and Mann–Whitney U test was used.
- Comparison between >2 qualitative variables e.g. (when a quantitative variable was grouped) and ≥1 quantitative variable(s): Analysis of variance (ANOVA) was used. When a significant difference was found a post hoc test needed to be performed in order to find out the groups among which the significant difference was. Afterward, as the sample used in this study is small, non-parametric tests needed to be performed and Kruskal–Wallis H test was used.
- Comparison between quantitative variables: Student's t-test was used. As the sample used in this study is small, non-parametric tests needed to be performed and Wilcoxon test was used.

Additionally, in order to perform the comparative analysis explained in 4.2.6. a database was provided by the director of this study in which patients that met criteria for AS but did not undergo AS were included. The reason for this is that the database included IIEF questionnaires before RRP and 3, 6, 12 and 24 months after RRP.

4. RESULTS

For a better understanding of the results, variables have been grouped in the following: Patient profile; prostate biomarkers; diagnostic biopsy and anatomopathological results; and quality of life questionnaires.

4.1. DESCRIPTIVE ANALYSIS

In order to clarify the descriptive analysis done in this study, all descriptive results have been summarized divided in the previously mentioned groups. (See **Table 10**)

Table 10. Descriptive results. This table shows the descriptive results divided in patient profile; prostate biomarkers; diagnostic biopsy and anatomopathological results; and quality of life questionnaires.

Variable (n)	n (%)
Patient Profile	
1. Age (n=53)	
a. ≤55	1 (1.9%)
b. 56-64	16 (30.2%)
c. ≥65	36 (67.9%)
2. BMI (n=52)	
a. <25	18 (34.62%)
b. [25-30)	26 (50%)
c. ≥30	8 (15.38%)
3. ECOG Performance Status (n=53)	
a. 0	46 (86.79%)
b. 1	7 (13.2%)
4. Charlson Comorbidity Index (n=53)	
a. 1	3 (5.7%)
b. 2	5 (9.4%)
c. 3	12 (22.6%)
d. 4	9 (17%)
e. 5	9 (17%)
f. 6	5 (9.4%)
g. 7	7 (13.2%)
h. 8	1 (1.9%)
i. 9	1 (1.9%)
j. 11	1 (1.9%)
5. PC Family History (n=51)	
a. No	40 (78.43%)
b. First-degree relative	10 (19.6%)
c. Third-degree relative	1 (1.96%)
6. Medical treatment (n=53)	
a. No	4 (7.54%)
b. Medical treatment but no alpha-blockers, 5-alpha reductase inhibitors and statins.	10 (18.86%)
c. Only alpha-blockers	9 (16.98%)
d. Alpha-blockers and statins	11 (20.75%)
e. Only statins	17 (32.07%)
f. Only 5-alpha reductase inhibitors	1 (1.88%)
g. Alpha-blockers, statins and 5-alpha reductase inhibitors	1 (1.88%)
7. Prostate surgical treatment prior to PC diagnosis (n=53)	
a. No	52 (98.11%)
b. Yes	1 (1.88&): retropubic adenomectomy
Prostate biomarkers	
1. Total PSA (n=53)	
a. ≤5 ng/ml	18 (33.96%)
b. (5-10] ng/ml	34 (64.15%)
c. >10 ng/ml	1 (1.89%)
2. PSA density (n=53)	
a. <0.15 ng/ml/cc	32 (60.37%)
b. ≥0.15 ng/ml/cc	21 (39.62%)
3. Free PSA / Total PSA (n=46)	
a. <10 %	6 (13%)
b. [10-20) %	22 (47.8%)
c. ≥20 %	18 (39.1%)
Staging	

1. Clinical stage (n=53)	
a. cT1c	39 (73.6%)
b. cT2a	13 (24.5%)
c. cT2c	1 (1.9%)
2. mpMRI (n=9)	
a. No suspicious	4 (44.44%)
b. Suspicious (not categorized with PIRADS)	2 (22.22%)
c. PIRADS 3	2 (22.22%)
d. PIRADS 4	1 (11.11%)
Diagnostic biopsy and anatomopathological results	
1. Biopsy technique (n=53)	
a. Cognitive targeted biopsy	3 (5.66%)
b. MRI/TRUS fusion software-based targeted biopsy	2 (3.77%)
c. TRUS guided biopsy	48 (90.56%)
2. Number of biopsies before diagnosis (n=53)	
a. 0	36 (67.9%)
b. 1	13 (24.5%)
c. 2	4 (7.5%)
3. Percentage of positive cylinders (n=53)	
a. ≤10 %	30 (56.6%)
b. (10-20] %	21 (39.62%)
c. >20 %	2 (3.77%)
4. Gleason score (n=53)	
a. 3 + 3	52 (98.12%)
b. 3 + 4	1 (1.88%)
5. Larger length affecting a cylinder (n=52)	
a. ≤1 mm	26 (50%)
b. >1 mm	26 (50%)
6. HGPIN presence (n=53)	
a. No	34 (64.2%)
b. Diagnosis biopsy	14 (26.4%)
c. Previous biopsies	4 (7.5%)
d. Diagnosis and previous biopsies	1 (1.9%)
7. ASAP presence (n=53)	
a. No	48 (90.6%)
b. Yes	5 (9.4%)
8. HGPIN + ASAP presence	1
Quality of Life Questionnaires	
1. IPSS (n=24)	
a. Mild symptoms	12 (50%)
b. Moderate symptoms	8 (33.3%)
c. Severe symptoms	4 (16.7%)
2. IPSS (n=24)	
a. Satisfied with symptoms	18 (75%)
b. Unsatisfied with symptoms	6 (25%)
3. CAVIPRESS (n=25)	
a. Very bad QOL	2 (8%)
b. Bad QOL	8 (32%)
c. Average QOL	10 (40%)
d. Good QOL	5 (20%)
4. IIEF (n=23)	
a. Unable to analyze (<5 points)	1 (4.3%)
b. Severe ED	3 (13%)
c. Moderate ED	3 (13%)
d. Mild ED	15 (65.4%)
e. No ED	1 (4.3%)

4.1.1. Patient profile

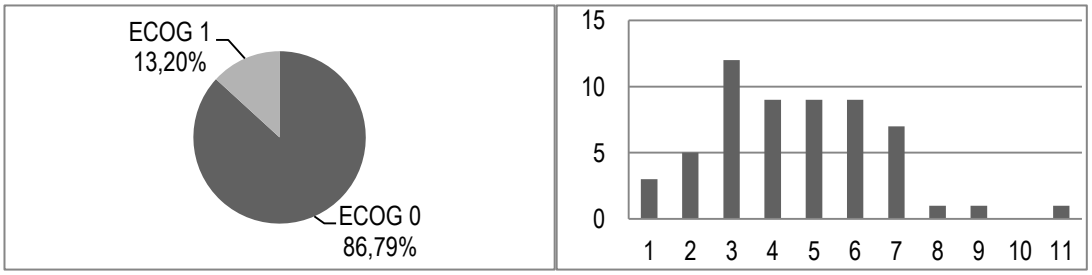
Most of the patients were above or 65 years old at diagnosis (67.9%), followed by those who were 56-64 years old (30.2%) and with a single case under 55 years (1.9%); the mean age was 68.11 years. (See: **Figure 2**)

Half of the patients were overweight (BMI 25-30 50%) according to the BMI WHO classification; the rest of the patients were classified as normal weight (BMI 18.5-25: 34.62%) or obese (BMI >30: 15.38%). It must be said that BMI couldn't be obtained in one case as it was not included in the medical record. (See: **Figure 3**)

Figures 2 and 3: Age and BMI. Figure 2 shows distribution of the age and Figure 3 shows distribution of patients regarding the BMI.

Regarding ECOG Performance Status, 46 patients (86.79%) were classified as "ECOG 0" while 7 (13.2%) as "ECOG 1". (See: **Figure 4**)

Charlson Comorbidity Index score results showed a wider variety. The most repeated score was 3 (12 patients) and it is remarkable that 10 patients had a score of 7 or more, meaning that their estimated 10-year survival was 0%. (See: **Figure 5**)



Figures 4 and 5: ECOG and CCI. Figure 4 shows distribution of patients regarding the ECOG score and Figure 5 shows distribution of patients regarding the CCI score.

There were 11 patients that had prostate cancer family history: 10 cases of first-degree relatives and 1 case of third-degree relatives.

Regarding medical treatment, 49 patients were having some kind of treatment when diagnosed: 22 patients were under alpha-blockers, 2 patients were under 5-alpha reductase inhibitors and 28 patients were under statins.

A deeper analysis was done related to the medical treatment:

- 10 patients did follow a medical treatment which didn't involve alpha-blockers, 5-alpha reductase inhibitors and statins
- 9 patients took only alpha-blockers
- 11 patients took alpha-blockers and statins simultaneously
- 17 patients took only statins
- 1 patient took only 5-alpha reductase inhibitors
- 1 patient took alpha-blockers, statins and 5-alpha reductase inhibitors simultaneously

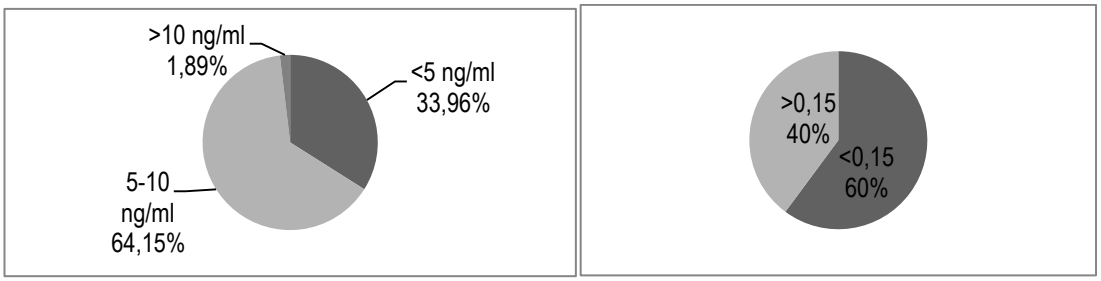
Thus, 22 patients were under prostate-targeted medical treatment.

Regarding prostate surgical treatment, only 1 patient underwent surgical treatment prior to PC diagnosis, retropubic adenomectomy precisely.

4.1.2. Prostate biomarkers

The mean of the total PSA when PC was diagnosed was 6.04 ng/ml. Most of the patients (64.15%) had a PSA between 5-10 ng/ml with just a patient (1.89%) with a PSA over 10 ng/ml. The mean PSA for patients <5 ng/ml (33.96%) was 4.51 ng/ml, for patients 5-10 ng/ml was 6.5 ng/ml and for the patient above 10 ng/ml was 18 ng/ml. (See: **Figure 6**)

Regarding PSA density the mean was 0.14 being 60.37% (32 patients) of the patients under 0.15. The mean among patients with a PSA density lower than 0.15 was 0.09 and among those with a PSA above 0.15 (39.62% / 21 patients) was 0.22. (See: **Figure 7**)



Figures 6 and 7: PSA and PSA density. Figure 6 shows distribution of patients regarding PSA and Figure 7 shows the distribution of patients regarding PSA density.

The mean Free PSA / Total PSA was 17.96%. The variable couldn't be obtained from 7 patients (13.2%), as not all the blood test show the result for free PSA. Thus, most of the patients for which the variable was obtained were classified with a Free PSA / Total PSA between 10% and 19% (41.5%). (See: **Figure 8**)

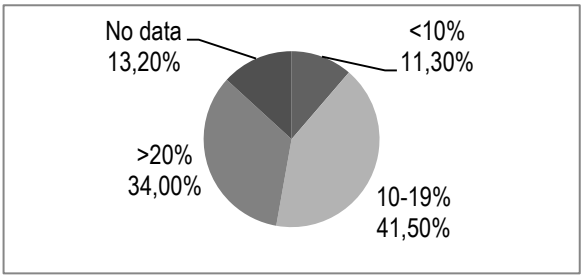
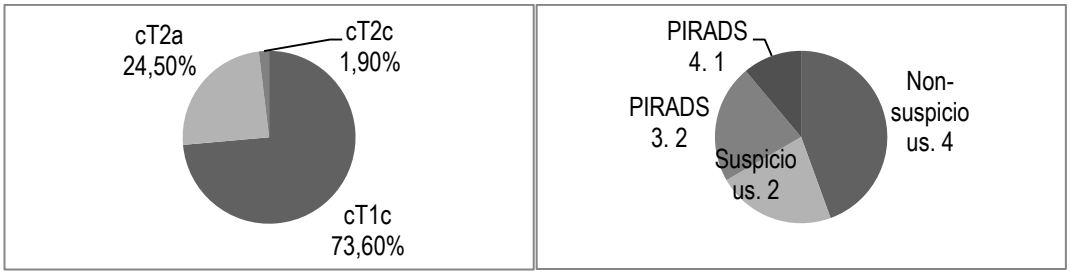


Figure 8: Free PSA / Total PSA. This figure shows distribution of patients regarding Free PSA / Total PSA.

4.1.3. Staging

At diagnosis, most of the patients' clinical stage was cT1c (39 patients/73.6%), 13 patients' (24.5%) stage was cT2a and there was only one patient (1.9%) whose clinical stage was cT2c. (See: **Figure 9**)

Multiparametric magnetic resonance imaging was used in 9 patients with results as follow: 4 patients showed a non-suspicious image, 2 patients showed a suspicious image (not categorized with PIRADS), 2 patients showed an image categorized as PIRADS 3, 1 patient showed an image categorized as PIRADS 4. (See: **Figure 10**)



Figures 9 and 10: Clinical Stage adn mpMRI. Figure 9 shows the distribution of patients regarding their clinical stage and Figure 10 shows the result of mpMRI.

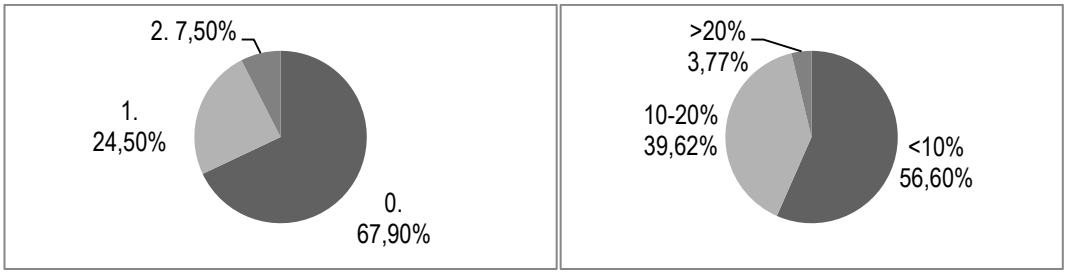
4.1.4. Diagnostic biopsy and anatomopathological results

In most of the patients (36 patients/67.9%) prostate cancer was diagnosed with the first biopsy, continued by those who had had a previous biopsy (24.5%). Lastly, there were 4 patients (7.5%) that had 2 previous biopsies prior to PC diagnosis. (See: **Figure 11**)

In the patients that mpMRI showed a suspicious but not PIRADS-categorized image and in the patient whose image was categorized as PIRADS 4, biopsy was obtained using the cognitive targeted biopsy technique (3patients).

In the 2 patients that showed an image categorized as PIRADS 3 mpMRI/TRUS fusion software-based targeted biopsy technique was used. TRUS guided biopsy technique was used in the remaining 48 patients.

Respecting the percentage of positive cylinders at diagnosis, the mean was 11.81% positive cylinders. In most of the patients less than 10% of the obtained cylinders were positive for tumor-tissue (30 patients/56.6%), followed by those with 10-20% of their cylinders being positive (21 patients/39.62%). Only in two patients (3.77%) more than 20% of the obtained cylinders were positive at diagnosis (being maximum 30%). (See: **Figure 12**)

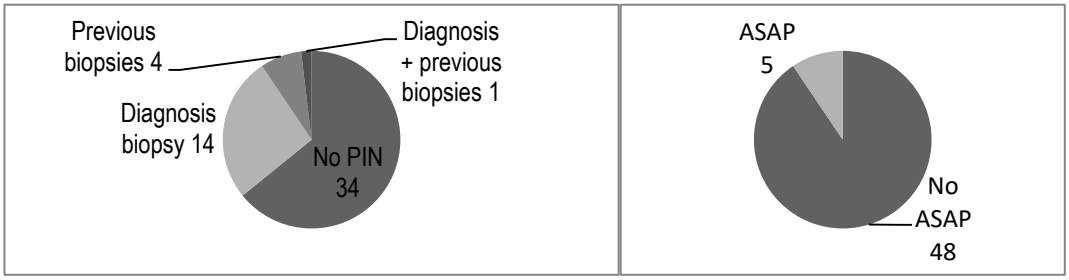


Figures 11 and 12: Number of previous biopsies and percentage of positive cylinders. Figure 11 shows the distribution of patients regarding the number of biopsies they had before the diagnostic biopsy and Figure 12 shows distribution of patients regarding the percentage of positive cylinders.

Regarding Gleason score, 1 patient was categorized as having a "3+4" grade tumor while the rest of the patients were categorized as having a "3+3" grade tumor.

Respecting the larger length affecting a cylinder, it is remarkable that exactly in half of the patients it was 1mm or less than 1mm and in the other half more than 1mm. In 1 patient this variable couldn't be obtained from the anatomopathological report.

HGPIN was seen in 19 patients as follows: 14 in the diagnosis biopsy, 4 in previous biopsies and 1 patient in which HGPIN was detected in both the diagnosis biopsies and previous biopsies. Regarding ASAP, it was seen in 5 biopsies. It must be pointed out that in one case HGPIN + ASAP was detected in previous biopsies. Additionally, perineural invasion was found in only one patient, who did not show PIN or ASAP. (See: **Figures 13 and 14**)

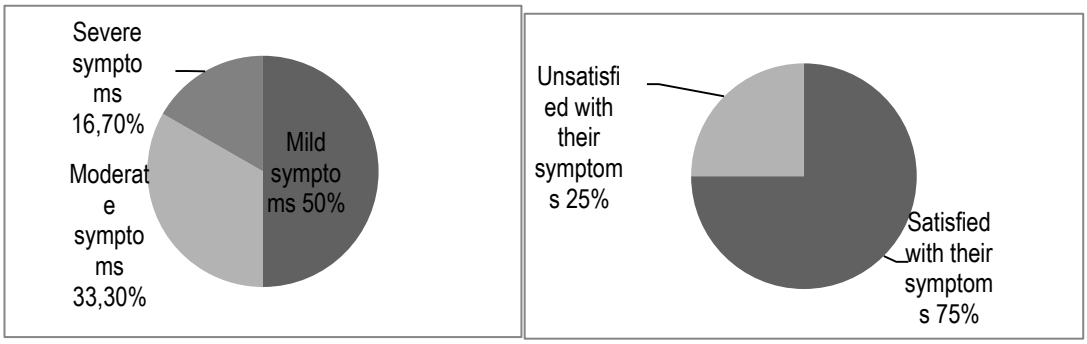


Figures 13 and 14: HGPIN and ASAP. Figure 13 shows distribution of patients regarding the presence of PIN and Figure 14 shows the distribution of patients regarding the presence of ASAP.

4.1.5. Quality of Life Questionnaires

As for quality of life questionnaires 14 IPSS, 14 CAVIPRES and 11 IIEF questionnaires were collected when diagnosed. Additionally, 10 IPSS, 11 CAVIPRES and 12 IIEF questionnaires were collected during follow-up, adding up to a total of 24 IPSS, 25 CAVIPRES and 23 IIEF questionnaires.

Concerning IPSS questionnaire, half of the patients (12 patients/50%) showed mild prostate-symptoms when diagnosed and during follow-up, 8 patients (33.3%) showed moderate symptoms and 4 patients (16.7%) showed severe symptoms. Moreover, 18 (75%) of those patients showed to be satisfied with their symptoms, including 8 patients that had the minimum punctuation in the 8th question, whereas 6 patients (25%) showed to be unsatisfied with their symptoms, including 2 patients that had the maximum punctuation in the 8th question. (See: **Figures 15 and 16**)

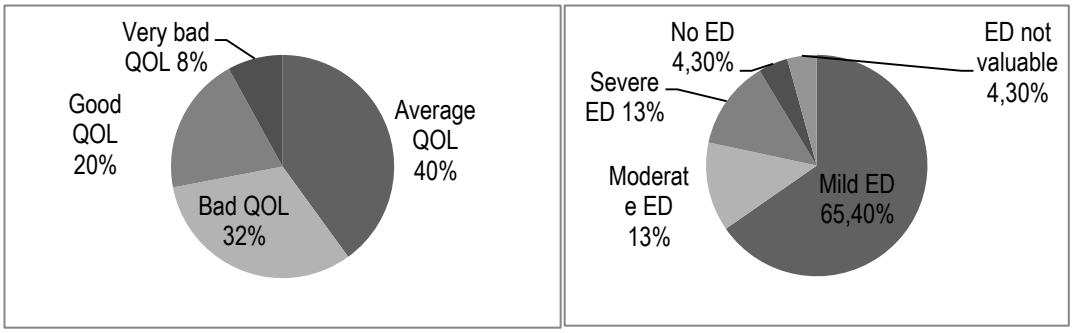


Figures 15 and 16: IPSS questions 1-7 and IPSS question 8. Figure 15 shows distribution of patients regarding the result in IPSS questionnaire's questions 1 to 7 and Figure 16 shows distribution of patients regarding the result in IPSS questionnaire's question 8.

Concerning CAVIPRES questionnaire, 10 patients (40%) showed an average quality of life, followed by 8 patients (32%) that showed a bad QOL, 5 patients (20%) showed a good QOL and, finally, 2 patients (8%) showed a very bad QOL. (See: **Figure 17**)

Regarding IIEF questionnaire, most of the patients (15 patients / 65.4%) showed to have a mild Erectile Dysfunction (ED), moderate and severe ED was seen in 3 patients (13%) each and 1 (4.3%) patient did not show ED at any degree.

Additionally, ED couldn't be analyzed on a patient as his punctuation was of less than 5 points. (See: **Figure 18**)



Figures 17 and 18: CAVIPRESS and IIEF. Figure 17 shows distribution of patients regarding the result in CABIPRESS questionnaire and Figure 18 shows distribution of patients regarding the result in IIEF questionnaire.

4.1.6. Progression and active treatment

11 of the 53 patients included into this sample have been actively treated.The decision to switch to active treatment was made based on the following reasons: (See **Figure 19)**

- Pathologic progression: 7 patients
- Local progression + metastatic progression: 1 patient
- Metastatic progression: 1 patient
- Agreement between doctor and patient: 2 patients

The mean time from the diagnosis until active treatment was done was 17 months, and most of the patients where followed-up 3 times in those 17 months.

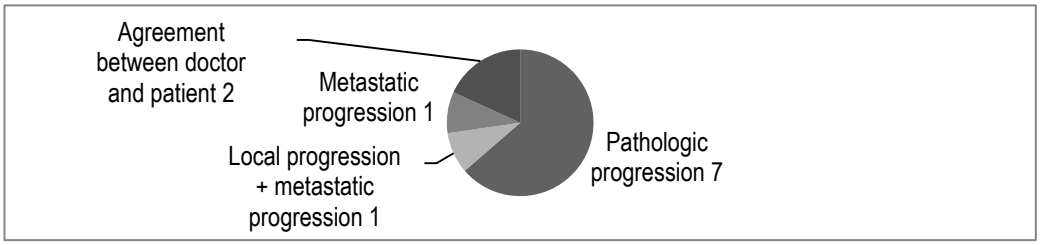


Figure 19: Reasons to switch to active treatment. This figure shows the distribution of the reasons to switch to active treatment.

The patients underwent active treatment as follows: 6 patients underwent Robotic Radical Prostatectomy (RRP), 4 patients underwent external beam radiotherapy and 1 patient underwent brachytherapy.

It is remarkable that during the follow-up 2 patients had pathologic progression and were advised to switch to active treatment but they refused.

4.1.7. Robotic radical prostatectomy

As it can be seen in **Table 11**, some differences were found after RRP was done once the decision to switch to active treatment was taken. In half of the patients (3 patients/50%) Gleason score increased from "3+3" to "3+4". All patients that had a cT1 stage were reclassified as pT2 stage, as pathological TNM does not include T1; thus, it can be said that their stage did not increase. Additionally, no tumoral lymph nodes were found in the 2 cases that lymphadenectomy was performed. The patient with the most advanced stage before RRP (cT2c) did increase his stage to pT3a.

Table 11. Gleason Score and TNM before and after RRP. RRP= Robotic Radical Prostatectomy.

	Gleason before RRP	Gleason after RRP	TNM before RRP	TNM after RPP
1	3 + 3	3 + 3	cT1c	pT2 pNx
2	3 + 3	3 + 3	cT1c	pT2 pN0
3	3 + 3	3 + 4	cT1c	pT2 pNx
4	3 + 3	3 + 4	cT1c	pT2 pNx
5	3 + 3	3 + 3	cT1c	pT2 pNx
6	3 + 3	3 + 4	cT2c	pT3a pN0

4.2. COMPARATIVE ANALYSIS

In order to perform the comparative analysis the variables described in **Table 5** were compared between the patients that had progression during their follow-up and the patients that did not have any progression during follow-up.

4.2.1. Patient profile

Patients with PC progression showed a higher age when PC diagnosis was done (1.89 years higher). Nonetheless, this difference is not statistically significant (p=0.286). (See: **Table 12**)

Table 12. Age at diagnosis related to progression.

	Progression	N	Mean	Standard Deviation	*p*
Age at diagnosis	No	40	67.65	6.731	0.286
	Yes	13	69.54	5.270	

Patients with PC progression showed a higher BMI when PC diagnosis was done (0.50 higher). Nonetheless, this difference is not statistically significant (p=0.363). (See: **Table 13**)

Table 13. BMI related to progression.

	Progression	N	Mean	Standard Deviation	*p*
BMI	No	39	26.43	3.48	0.363
	Yes	13	26.93	4.27	

Most of the patients with PC progression were classified as ECOG 0, as well as most of the patients with no progression. No statistically significant difference was found between ECOG and progression (p=0.499). (See: **Table 14**)

Table 14. ECOG related to progression.

		ECOG		Total	*p*
		0	1		
Progression	No	34	6	40	0.499
	Yes	12	1	13	
Total		46	7	53	

Patients with PC progression showed a higher Charlson Score when PC diagnosis was done (1.31 higher). Moreover, this difference is statistically significant (p=0.011). (See: **Table 15**)

Table 15. Charlson score related to progression.

	Progression	N	Mean	Standard Deviation	*p*
Charlson Score	No	40	4.15	2.22	0.011
	Yes	13	5.46	1.26	

Most of the patients with PC progression did not have PC family history, as well as most of the patients with no progression. No statistically significant difference was found between PC family history and progression (p=0.202). (See: **Table 16**)

Table 16. Prostate cancer family history related to progression.

		PC Family History		Total	*p*
		No	Yes		
Progression	No	29	10	39	0.202
	Yes	11	1	12	
Total		40	11	51	

Most of the patients with PC progression did not take alpha-blockers, as well as most of the patients with no progression. No statistically significant difference was found between treatment with alpha-blockers and progression (p=0.797). (See: **Table 17**)

Table 17. Treatment with alpha-blockers related to progression.

		Treatment with alpha-blockers		Total	*p*
		No	Yes		
Progression	No	23	17	40	0.797
	Yes	8	5	13	
Total		31	22	53	

Most of the patients with PC progression did not take 5-alpha reductase inhibitors, as well as most of the patients with no progression. No statistically significant difference was found between treatment with 5-alpha reductase inhibitors and progression (p=0.393). (See: **Table 18**)

Table 18. Treatment with 5-alpha reductase inhibitors related to progression.

		Treatment with 5-alpha reductase inhibitors		Total	*p*
		No	Yes		
Progression	No	39	1	40	0.393
	Yes	12	1	13	
Total		51	2	53	

Most of the patients with PC progression did not take statins, but most of patients with no progression did take statins. Nevertheless, no statistically significant difference was found between treatment with statins and progression (p=0.232). (See: **Table 19**)

Table 19. Treatment with statins related to progression.

		Treatment with statins		Total	*p*
		No	Yes		
Progression	No	17	23	40	0.232
	Yes	8	5	13	
Total		25	28	53	

4.2.2. Prostate biomarkers

Patients with PC progression showed a lower total PSA level when PC diagnosis was done (0.38 ng/ml lower). Nonetheless, this difference is not statistically significant (p=0.788). (See: **Table 20**)

Table 20. Total PSA related to progression.

	Progression	N	Mean	Standard Deviation	*p*
Total PSA	No	40	6.14	2.48	0.788
	Yes	13	5.75	1.26	

Patients with PC progression showed a lower PSA density when PC diagnosis was done (0.033 lower). Nonetheless, this difference is not statistically significant (p=0.174). (See: **Table 21**)

Table 21. PSA density related to progression.

	Progression	N	Mean	Standard Deviation	*p*
PSA density	No	40	0.156	0.089	0.174
	Yes	13	0.122	0.076	

Patients with PC progression showed a higher Free PSA / Total PSA level when PC diagnosis was done (3.1% higher). Nonetheless, this difference is not statistically significant (p=0.197). (See: **Table 22**)

Table 22. Free PSA / Total PSA related to progression.

	Progression	N	Mean	Standard Deviation	*p*
Free PSA / Total PSA	No	34	17.15	7.059	0.197
	Yes	12	20.25	7.569	

4.2.3. Clinical stage

Most of the patients with PC progression were classified as cT1c stage, as well as most of the patients with no progression. No statistically significant difference was found between clinical stage and progression (p=0.158). (See: **Table 23**)

Table 23. Clinical stage related to progression.

		Clinical stage			Total	*p*
		cT1c	cT2a	cT2c		
Progression	No	29	11	0	40	0.158
	Yes	10	2	1	13	
Total		39	13	1	53	

4.2.4. Diagnostic biopsy and anatomopathological results

Most of the patients with PC progression were diagnosed with PC on their first biopsy, as well as most of the patients with no progression. No statistically significant difference was found between the number of biopsies before PC was diagnosed and progression (p=0.673). (See: **Table 24**)

Table 24. Number of previous biopsies related to progression.

		Number of previous biopsies			Total	*p*
		0	1	2		
Progression	No	26	11	3	40	0.673
	Yes	10	2	1	13	
Total		36	13	4	53	

Patients with PC progression showed a lower percentage of positive cylinders when PC diagnosis was done (0.345% lower). Nonetheless, this difference is not statistically significant (p=0.699). (See: **Table 25**)

Table 25. Percentage of positive cylinders related to progression.

	Progression	N	Mean	Standard Deviation	*p*
Percentage of positive cylinders	No	40	11.89	5.29	0.699
	Yes	13	11.54	5.48	

Patients with PC progression showed a smaller "larger length affecting a cylinder" when PC diagnosis was done (0.21mm lower). Nonetheless, this difference is not statistically significant (p=0.694). (See: **Table 26**)

Table 26. Larger length affecting a cylinder related to progression.

	Progression	N	Mean	Standard Deviation	*p*
Larger length affecting a cylinder	No	39	2.064	1.70	0.694
	Yes	13	1.846	1.29	

In most of the patients with PC progression HGPIN was not found in the biopsies, as well as in most of the patients with no progression. No statistically significant difference was found between HGPIN and progression (p=0.459). (See: **Table 27**)

Table 27. HGPIN related to progression.

		HGPIN				Total	*p*
		No	Diagnosis biopsy	Previous biopsies	Diagnosis and previous biopsies		
Progression	No	26	9	4	1	40	0.459
	Yes	8	5	0	0	13	
Total		34	14	4	1	53	

In most of the patients with PC progression ASAP was not found in the biopsies, as well as in most of the patients with no progression. No statistically significant difference was found between ASAP and progression (p=0.180). (See: **Table 28**)

Table 28. ASAP related to progression.

		ASAP		Total	*p*
		No	Yes		
Progression	No	35	5	40	0.180
	Yes	13	0	13	
Total		48	5	53	

4.2.5. Robotic radical prostatectomy

Table 30 shows the comparison on IIEF score before RRP and 3, 6, 12 and 24 months after RRP. It can clearly be said that in all cases IIEF scores decreases after RRP was done. The most notorious case is after 18 months, in which the score decreases 15.8 points. Moreover, these differences are statistically significant in all cases but after 18 months.

Table 30. IIEF score comparison between before RRP and after RRP: 3, 6, 12, 18 and 24 months after.

		N	Mean	Standard Deviation	*p*
Before RRP & 3 months after	Before RRP	18	23.67	8.289	<0.001
	3 months after	18	11.00	9.870	
Before RRP & 6 months after	Before RRP	15	20.87	9.141	0.003
	6 months after	15	10.67	9.597	
Before RRP & 12 months after	Before RRP	16	24.13	7.751	0.004
	12 months after	16	14.56	10.469	
Before RRP & 18 months after	Before RRP	5	28.60	3.130	0.066
	18 months after	5	12.80	11.100	
Before RRP & 24 months after	Before RRP	7	24.29	9.776	0.042
	24 months after	7	20.86	11.276	

5. DISCUSSION

The inclusion criteria for AS vary depending on the protocol, some of them being more strict than others. In order to unify criteria in 2017 an AS protocol was implemented in Basurto University Hospital with strict criteria. In this study it has been observed that only 16 patients (30.18%) included in the sample that has been studied since 2014, met the inclusion criteria found in the Basurto University Hospital AS protocol, implemented in 2017.

However, if we take the PRIAS[45] study's protocol (See **Table 5**) as reference, 49 patients would meet the inclusion criteria. The reason why more patients met the criteria for AS using this protocol is that it does not include an estimated survival of more than 10 years as an inclusion criterion.

Finally, if we take into account the AEU-PIEM protocol (Total PSA <10 ng/ml, stage ≤T3, minimum 10 cylinders obtained in biopsy, maximum 3 positive cylinders, Gleason grade ≤3+4) all patients would meet the criteria. Nevertheless, it must be said that this protocol is a sole protocol designed for investigation and not to be applied in clinical practice.

Furthermore, based on the fact that AS is a deferred but curative treatment modality, only cases in which treatment would mean an improvement to the patient's estimated survival should be considered for AS. Thus, in this sample 24 patients had a Charlson score of ≥5, which should exclude them from AS and include them into Watchful Waiting protocols. Additionally, Charlson score should be calculated in every follow-up with the goal of detecting when the patient's estimated survival decreases and, in this way, avoid overtreatment.

Most of the sample's patients were above or 65 years old at diagnosis, following the line of epidemiological data regarding PC[59]. When it comes to associating age with progression, patients included in this paper with PC progression showed a higher age when PC diagnosis was done, although it was not statistically significant. It is not clear though, whether age and progression are related[60, 61].

Almost half of the patients were overweight; similarly, BMI was higher among those with PC progression, despite not being statistically significant. Scientific literature states that obesity is relatively and consistently associated with a higher risk of aggressive prostate cancer[62] as well as with increased risk of PC mortality and recurrence[63].

Although most of the patients were classified as "ECOG 0" 24 patients had a Charlson score of ≥5, which should exclude them from AS and include them into Watchful Waiting protocols due to the fact that in order to follow an AS protocol a patient must have an estimated survival above 10 years according to most guidelines. That been said, and as it has been mentioned before, the use of Charlson Comorbidity Index score could be beneficial with the objective of determining a patient's estimated 10-year survival.

Despite most clinicians use CCI to determine a patient's survival estimation, no study has analyzed the relation of CCI score with prostate cancer's progression. In

this study that has been performed and, surprisingly, statistically significant difference has been proved between patients with no progression and with progression: patients whose PC progressed had a higher CCI score. This means that patients with a lower life expectancy had a higher risk of having their PC progress. This is something that has never been described before but as the sample included in this study is quite small, further investigation upon this result must be performed.

Notwithstanding the fact that there was only one patient that progressed and had PC family history, studies state that certain genes have been related to more aggressive forms of PC[63].

Some articles associate alpha-blocker users with a higher risk of high-grade PC[64]. More recent studies prove that alpha-blockers can be used as chemopreventive agents in PC and they support that these drugs induce apoptosis-mediated suppression of prostate tumor growth and metastasis[65]. In this study, most of the patients that were users of alpha-blockers did not progress, but that difference is not statistically significant.

The use of 5-alpha reductase inhibitors cannot be analyzed in this study as only 2 patients took them. However, these drugs have the potential of preventing or delaying the development of PC[66].

Statins have been associated as being pre-clinical potential chemo-preventive agents, although more and larger studies must be performed[67]. Another study has stated that statin use at diagnosis was not significantly protective against pathological or therapeutic progression in men undergoing AS[68]. In this paper no statistically significant difference has been found between those who took statins and those who did not regarding progression.

Most AS protocols include the measurement of PSA on follow-up in order to determine progression. It is normally not done directly based on the total PSA but on the PSA doubling time (although this variable has not been included in this study) [69]. It is interesting to remark that in this study patients with progression showed a lower total PSA level despite the fact that the difference is not statistically significant.

PSA density is a strong predictor of adverse pathological features and biochemical recurrence after radical treatment[7]. Thus, it is taken into account to determine

eligibility for AS. As it has been explained before, 21 patients had a PSA density of more than 0.15, which is the cut-off point for higher pathological features and biochemical recurrence after radical treatment[11]. Once again, this study shows rare results as the PSA density is higher on those patients with no progression in spite of the difference not being statistically significant.

AS said before, Free PSA / Total PSA is of no clinical use if the total serum PSA is > 10 ng/mL or during follow-up of known PC[3]. In this study patients with progression showed a higher F/T PSA but the difference is not statistically significant; hence agreeing with the previous statement.

Clinical stage is directly related to PC progression; in fact, the more advanced the stage is the more chances for progression there are. Most protocols include cT2 stage into AS but not cT3. In this study as most of patients were cT1c stage, no statistically significant difference was found.

Results show how most of the patients were diagnosed with PC on their first biopsy. This means that good professional decision was taken regarding the moment when a biopsy needed to be taken. Still, 17 patients needed to have more than a biopsy taken in order to be diagnosed. The EAU guidelines supports the use of mpMRI and several tests (Progensa, SelectMDX, PHI, 4Kscore Test, ConfirmMDX) in order to decide whether a new biopsy is needed; it must be said that the FDA has only approved the Progenasa test and that all these mentioned tests are not available in our area.

The percentage of positive cylinders and the larger length affecting a cylinder in the diagnosis biopsy have been related to treatment-free time[70] and thus to progression. In this study the percentage of positive cylinders among patients that progressed was higher, agreeing with the previous statement; nonetheless, no statistically significant difference was found. Contrarily, in this study the mean of the larger length affecting a cylinder was higher in patients with no progression but no statistically significant difference was found either.

Several studies have associated the presence of HGPIN and ASAP in a negative biopsy with the need for a new biopsy[20, 21, 22, 23] but no association has been done

between HGPIN, ASAP and PC progression and in this study no relation has been found either.

Lastly and in order to see the deterioration of quality of life after RRP, which would justify the use of active surveillance as treatment modality, IIEF was used. As expected[71], worsening of the symptoms followed the RRP, being the difference statistically significant.

One of the problems that was faced during the data collection was the lack of information on some of the medical records. For instance, QOL during the follow-up wanted to be analyzed but it was not possible, as only patients with recent PC diagnosis had filled QOL questionnaires at different points of the follow-up. Additionally, the 6 patients that underwent RRP had not all answered QOL questionnaires after they had been operated. Race, living area, education level, marital status, employment status and physical activity habits variables couldn't be analyzed either as there was little information regarding those aspects.

The use of mpMRI/TRUS fusion software-based targeted biopsies could not be analyzed regarding progression, as it has recently been introduced in Basurto University Hospital.

As explained previously, Charlson Comorbidity Index Score is a method of predicting mortality by classifying or weighting comorbid conditions. Despite the extended use of that index, it should be pointed out that it was developed during the eighties. As medicine is constantly changing, this index should be validated too, so that it gives a mortality prediction that adjusts to the treatments and medicine of the time when it is used. An example to this, is that one of the variables that this index measures is the infection with human immunodeficiency virus, giving it 6 points, which means an estimated 10-year survival of ≤2%. This is not truthful, as treatment for human immunodeficiency virus infections has considerably improved since the development of this index.

6. CONCLUSIONS

It is necessary to establish common criteria among the scientific community in order to implement AS as a treatment modality and, thus, analyze long-term results.

The main reason why patients were deviated from the protocol is the estimated 10-year survival. Taking that into account, it can be concluded that those patients have been submitted to excessive follow-up and three of them to overtreatment.

That having been said, a strict selection of patients should be done when considering AS as a treatment option, specially focusing on the estimated 10-year survival.

The deferral of active treatment can be justified not only because of the indolent tumor in these patients but also by seeing the results obtained regarding QOL deterioration after RRP.

In this study's comparative analysis 2 variables had statistically significant difference when they were related to the presence of progression: CCI score (a higher score was seen on patients that had progressed), and lose of QOL after RRP (measured using IIEF).

This study should be extended in order to be able to include more patients into the database and, thus, obtain results that can be extrapolated to the general application of this treatment modality.

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ANNEX 1: GENETIC, EXTERNAL AND DIETARY RISK FACTORS

Table 31. Summary table of genetic factors, external risk factors and dietary factors associated with PC. (HPC: Hereditary Prostate Cancer) Source: Own elaboration.

Variation	Effect
Genetic factors	
ELAC2 (mapping to the HPC2)	Increases PC risk among Caucasians and Asian men, but not among African descendants
RNASEL (mapping to the HPC1)	D541E variant is associated with a twofold increased risk in Caucasians
MSR1 (mapping to 8p22-23)	Increases PC risk both in HPC and sporadic PC. When it is delated in prostate tumors it shows a moderate risk for PC. MSR1 Asp174Tyr mutation is more frequent in African descendants: higher PC risk
HOXB13	It is related to the regulation of critical steps in the development of the prostate. Its G84E variant seems to be one of the major germline mutations associated with high risk of HPC, especially among Caucasian descendants
BRCA1 and BRCA2	These tumor suppressor genes regulate DNA replication. Both of the genes are related to an increased risk of PC, notably in men younger than 65 years. While BRCA1 means a 4.5 higher risk of PC, BRCA2 means an 8.3 higher risk. BRAC2 mutations not only mean a higher risk of PC, but also an increased risk of high-grade tumor, progression to metastatic castrate resistant prostate cancer and 5 year cancer specific survival rates between 50% and 60%. Hence, BRCA2 mutations contribute more to higher risk of PC
MSH2, MLH1, PMS1, PMS2, MSH6	These genes are involved in DNA Mismatch Repair and are connected to Lynch Syndrome which is characterized by a higher risk of several tumors, notoriously, hereditary nonpolyposis colorectal cancer. Additionally, it has been proved that men that suffer from Lynch Syndrome have a double risk of developing PC compared to the general population
CHEK2 and ATM	These are involved in the DNA Damage Repair pathway and are also associated with a higher PC risk. Missense (a mutation in which a single nucleotide change results in a codon that codes for a different amino acid) variants of CHEK2 have been found in 3-10% of PCs and have been linked to a higher PC risk. Moreover, DNA repair gene mutations also increase the risk of advanced disease, metastatic spread and worse survival rate
CAG	There is a relation between shorter CAG repeat lengths and progression of PC. A CAG repeat length of 22 or shorter has been linked with a higher risk of PC and African descendants usually have shorter CAG repeats
Cytochrome gene family	These enzymes metabolize many substances such as testosterone and chemotherapeutic drugs. CYP3A4 is involved in the metabolism of testosterone and is associated with a higher grade PC in Caucasian men. Furthermore, CYP3A4*1B and CYP3A43*3 allelic combinations represent a protective role for early onset of PC. While only 4% of Caucasian men carry this combination 35% of African descendants have this haplotype. Thus, African descendants who carry that haplotype are less likely to develop early onset PC
External risk factors	
Obesity	Associated with lower risk of low-grade PC but increased risk of high-grade PC, as well as, with increased risk of PC mortality and recurrence
Height	Taller height is related to a higher risk of both overall and advanced disease PC. This might be explained by taking into account that an adult's height reflects early life exposure to growth hormones (IGF-1 for example). In addition, birth size is not associated with a higher PC risk, suggesting that the important time period for the etiology might be puberty, when the prostate undergoes maturation and rapid growth

Physical activity	Physical activity has an inverse association with the risk of advanced and fatal PC; what is more, it has been correlated to an improvement of survival and a decreased PC progression. It is not clear yet the mechanism which would explain these statements but studies have suggested that physical activity might act through changes in sex hormone levels, anti-inflammatory pathways, or the IGF axis
Smoking	Smoking increases risk of death from PC and risk of advanced disease and less differentiated tumor. Higher mortality might be due to the influence of smoking in the response to the treatment. To be more accurate, smoking increases PC mortality risk on a 60%. Additionally, it should be pointed out that that risk exist if an individual has been a smoker in the 10 previous years to the diagnosis of PC; thus, total lifetime smoking is not associated with a higher PC mortality risk
Cholesterol	There is no evidence to associate blood total cholesterol, HDL cholesterol and LDL cholesterol with the risk of PC and advanced disease PC
Metformin	The use of Metformin has been proved to reduce the risk of PC diagnosis
Ejaculation	Based on the "prostate stagnation hypothesis" which states that carcinogens accumulate in the prostate between ejaculations and affect cells' genome and metabolic processes, several studies have been made to correlate the ejaculation frequency with the risk of developing PC. It has been found that ejaculation frequency is associated with the reduction of developing PC
Dietary factors	
Lycopene and tomato-based products	Lycopenes accumulate in high concentration in prostatic tissue. Due to its antioxidant activity it avoids the oxidation of molecules (DNA and proteins) implicated in carcinogenesis. Studies have proved lycopene to reduce advanced and lethal PC, as well as overall PC but to a lesser extent.
Coffee	There is an inverse association between the coffee intake and the ocerall PC and high grade disease
Fish	Studies have shown a reduction in PC mortality when a higher total fish intake was provided
Alcohol	Heavy regular alcohol consumption and binge drinking patterns may be associated with increased prostate cancer risk, while abstinence may be associated with increased risk of prostate cancer-specific mortality compared to light alcohol consumption
Phytoestrogens	Phytoestrogen intake is associated with a reduced risk of PC
Dairy and meat products	No correlation has been found

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ANNEX 2: SCREENING RECOMMENDATIONS

European Association of Urology Guidelines

Table 32. EAU recommendation on PC screening. Source: EAU

Recommendations	Strength rating
Do not subject men to PSA testing without counselling them on the potential risk and benefits.	Strong
Offer an individualized risk-adapted strategy for early detention to a well-informed man with a good performance status and a life-expectancy of at least ten to fifteen years.	Strong
Offer early PSA testing in well-informed mean at elevated risk of having PC: • Men >50 years of age; • Men >45 years of age and family history of PC; • African-Americans >45 years of age.	Strong
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of two years for those initially at risk: • Men with a PSA level of >1 ng/ml at 40 years of age; • Men with a PSA level of >2 ng/ml at 60 years of age; Postpone follow-up to eight years in those not at risk.	Weak
Stop early diagnosis of PC based on life expectancy and performance status; men who have a life-expectancy of < fifteen years are unlikely to benefit.	Strong

American Urological Association

1. The Panel recommends against PSA screening in men under age 40 years. (*Recommendation*; Evidence Strength Grade C)
2. The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk. (*Recommendation*; Evidence Strength Grade C)
3. For men ages 55 to 69 years the Panel recognizes that the decision to undergo PSA screening involves weighing the benefits of reducing the rate of metastatic prostate cancer and prevention of prostate cancer death against the known potential harms associated with screening and treatment. For this reason, the Panel strongly recommends shared decision-making for men age 55 to 69 years that are considering PSA screening, and proceeding based on a man's values and preferences. (*Standard*; Evidence Strength Grade B)
4. To reduce the harms of screening, a routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening. As compared to annual screening, it is expected that screening intervals of two years preserve the

majority of the benefits and reduce overdiagnosis and false positives. (*Option*; Evidence Strength Grade C)

5. The Panel does not recommend routine PSA screening in men age 70+ years or any man with less than a 10 to 15 year life expectancy. (*Recommendation*; Evidence Strength Grade C)

European Society for Medical Oncology

- Population-based PSA screening for prostate cancer reduces prostate cancer mortality at the expense of over diagnosis and overtreatment and is not recommended [I, C].
- Testing for prostate cancer in asymptomatic men should not be done in men over the age of 70 years [I, B].

American Cancer Society

The discussion about screening should take place at:

- Age 50 for men who are at average risk of prostate cancer and are expected to live at least 10 more years.
- Age 45 for men at high risk of developing prostate cancer. This includes African Americans and men who have a first-degree relative (father, brother, or son) diagnosed with prostate cancer at an early age (younger than age 65).
- Age 40 for men at even higher risk (those with more than one first-degree relative who had prostate cancer at an early age).

ANNEX 3: CHARLSON COMORBIDITY INDEX FORMULA

Addition of the selected points:

Variable	Definition	Points
Myocardial infarction	History of definite or probable MI (EKG changes and/or enzyme changes)	1
Congestive heart failure	Exertional or paroxysmal nocturnal dyspnea and has responded to digitalis, diuretics, or afterload reducing agents	1
Peripheral vascular disease	Intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or untreated thoracic or abdominal aneurysm (≥6 cm)	1
Cerebrovascular accident or transient ischemic attack	-	1
Dementia	Chronic cognitive deficit	1
Chronic obstructive pulmonary disease	-	1
Connective tissue disease	-	1
Peptic ulcer disease	Any history of treatment for ulcer disease or history of ulcer bleeding	1
Mild liver disease	Mild = chronic hepatitis (or cirrhosis without portal hypertension)	1
Uncomplicated diabetes	-	1
Hemiplegia	-	2
Moderate to severe chronic kidney disease	Severe = on dialysis, status post kidney transplant, uremia, moderate = creatinine >3 mg/dL (0.27 mmol/L)	2
Diabetes with end-organ damage	-	2
Localized solid tumor	-	2
Leukemia	-	2
Lymphoma	-	2

Moderate to severe liver disease	Severe = cirrhosis and portal hypertension with variceal bleeding history, moderate = cirrhosis and portal hypertension but no variceal bleeding history	3
Metastatic solid tumor	-	6
AIDS*	-	6

Plus 1 point for every decade age 50 years and over, maximum 4 points.

Note: liver disease and diabetes inputs are mutually exclusive (e.g. do not give points for both "mild liver disease" and "moderate or severe liver disease").

Formula:

10-year survival = 0.983^($e^{CCI \times 0.9}$), where CCI = Charlson Comorbidity Index

ANNEX 4: QUALITY OF LIFE QUESTIONNAIRES

IIEF (International Index of Erectile Function) Questionnaire

Write the number that best describes your erectile function for the past 4 weeks in the spaces provided.	
Over the past four weeks: 1. How often were you able to get an erection during sexual activity?	0 = No sexual activity 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	0 = No sexual activity 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
4. During intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
5. During sexual intercourse, how difficult was it to maintain your erection during intercourse?	0 = Did not attempt intercourse 1 = Extremely difficult 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
6. How would you rate your confidence that you could keep an erection?	1 = Very low 2 = Low 3 = Moderate 4 = High 5 = Very high
Total IIEF Score	
Clinical Interpretation	
Score	**Interpretation**
<5	Unable to analyze
6-10	Severe erectile dysfunction
11-16	Moderate erectile dysfunction
17-25	Mild erectile dysfunction
26-30	No erectile dysfunction

IPSS (International Prostate Symptom Score) Questionnaire

			Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1	**Frequency:** Over the past month, how often have you had to urinate again less than two hours after you finished urinating?		0	1	2	3	4	5
2	**Urgency:** Over the last month, how difficult have you found it to postpone urination?		0	1	2	3	4	5
3	**Incomplete:** emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?		0	1	2	3	4	5
4	**Intermittency:** Over the past month, how often have you found you stopped and started again several times when you urinated?		0	1	2	3	4	5
5	**Weak stream:** Over the past month, how often have you had a weak urinary stream?		0	1	2	3	4	5
6	**Straining:** Over the past month, how often have you had to push or strain to begin urination?		0	1	2	3	4	5
7	**Nocturia:** Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?		None 0	1 time 1	2 times 2	3 times 3	4 times 4	5 times or more 5
		Delighted	**Pleased**	**Mostly satisfied**	**Mixed: Equally satisfied / dissatisfied**	**Mostly dissatisfied**	**Unhappy**	**Terrible**
8	**Quality of life due to urinary symptoms:** If you were to spend the rest of your life with your urinary	0	1	2	3	4	5	6

	condition the way it is now, how would you feel about that?							

Clinical Interpretation	
Score (questions 1-7)	**Interpretation**
0-7	Mild symptoms
8-19	Moderate symptoms
20-35	Severe symptoms
Score (question 8)	**Interpretation**
0-2	Satisfied with symptoms
3-6	Unsatisfied with symptoms

CAVIPRES Questionnaire (not available in English)

Valore las siguientes situaciones, pensando en cómo se ha encontrado en las **últimas cuatro semanas**	EN LAS ÚLTIMAS CUATRO SEMANAS, ¿CON QUÉ **FRECUENCIA** SE HA ENCONTRADO CON ESTA SITUACIÓN?				
	Siempre	**Muchas veces**	**La mitad de las veces**	**Pocas veces**	**Nunca**
Aspectos psicológicos					
1. Mi enfermedad me preocupa.	1	2	3	4	5
2. Mi enfermedad me impide hacer una vida normal.	1	2	3	4	5
3. Pienso en mi enfermedad.	1	2	3	4	5
4. Necesito hablar de las preocupaciones o miedos que me causa mi enfermedad.	1	2	3	4	5
5. Me preocupa cómo evolucionará mi enfermedad.	1	2	3	4	5
6. Me preocupa encontrarme peor.	1	2	3	4	5
7. Mi enfermedad afecta negativamente a mi vida.	1	2	3	4	5

8. Me molesta que me consideren un enfermo de cáncer.	1	2	3	4	5
Esperanza y futuro					
9. Vivo el presente con ilusión.	1	2	3	4	5
10. Veo el futuro con optimismo.	1	2	3	4	5
11. A pesar de mi enfermedad, soy capaz de disfrutar de la vida.	1	2	3	4	5
12. Mi enfermedad hace que aprecie más algunas cosas de la vida.	1	2	3	4	5
Vida sexual					
13. Tengo problemas de erección.	1	2	3	4	5
14. Tengo problemas para alcanzar el orgasmo.	1	2	3	4	5
15. Tengo problemas para eyacular.	1	2	3	4	5
16. Siento que mi vida sexual se ha acabado debido a mi enfermedad.	1	2	3	4	5
17. He perdido el interés por el sexo a causa de mi enfermedad.	1	2	3	4	5
18. "Me quedo a medias" en mis relaciones sexuales.	1	2	3	4	5

Valore las siguientes situaciones, pensando en cómo se ha encontrado en las **últimas cuatro semanas**	EN LAS ÚLTIMAS CUATRO SEMANAS, ¿CON QUÉ **FRECUENCIA** SE HA ENCONTRADO CON ESTA SITUACIÓN?				
	Siempre	**Muchas veces**	**La mitad de las veces**	**Pocas veces**	**Nunca**
Apoyo social y pareja					
19. La familia me ayuda con mi enfermedad y su tratamiento.	1	2	3	4	5
20. A pesar de la enfermedad y sus consecuencias, me siento unido a mi pareja.	1	2	3	4	5
21. Aunque mi pareja me comprende, a mí me sigue preocupando mi problema de erección.	1	2	3	4	5
22. Mi pareja me ayuda y colabora para solucionar mis problemas sexuales.	1	2	3	4	5
23. Me siento entendido y apoyado por mis amigos.	1	2	3	4	5
24. Los profesionales sanitarios me apoyan respecto a mi problema de impotencia.	1	2	3	4	5

Indique su grado de acuerdo o desacuerdo con las siguientes afirmaciones teniendo en cuenta cómo se ha encontrado **en las últimas cuatro semanas**	¿EN QUÉ MEDIDA ESTÁ **DE ACUERDO O EN DESACUERDO** CON LAS SIGUIENTES AFIRMACIONES?				
	Totalmente de acuerdo	**De acuerdo**	**No estoy seguro**	**En desacuerdo**	**Totalmente en desacuerdo**
25. En general, creo que necesito más información sobre mi enfermedad.	1	2	3	4	5
26. En general, creo que debería haber recibido más información sobre las secuelas que me quedarían.	1	2	3	4	5
27. Me gustaría que hubiera un servicio de apoyo para las personas que tenemos esta enfermedad.	1	2	3	4	5
28. He tenido la necesidad de hablar de mi enfermedad con alguien.	1	2	3	4	5
29. Creo que intercambiar experiencias con otras personas me daría un poco más de confianza.	1	2	3	4	5
30. Me gustaría poder estar a solas con mi médico para preguntarle todas mis dudas.	1	2	3	4	5

Clinical Interpretation	
Score	**Interpretation**
30-54	Very bad QOL
55-78	Bad QOL
79-102	Average QOL
103-126	Good QOL
127-150	Very good QOL