

Biochemical Recurrence following Prostate Cancer definitive treatment in Brazil: A Retrospective Chart Review Study

Non-Interventional Final Study Report

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Research Question and Objectives	<p>This study aims to characterize the high-risk biochemical recurrence population after definitive treatment (radical prostatectomy or radiotherapy [including brachytherapy] ± hormone therapy, or both, with curative intent) in men with localized or locally advanced prostate cancer to define the history of biochemical relapse after the primary definitive treatment in the Brazilian real-world setting.</p> <p>The primary objective is to determine the 5-year BCR rate in men with localized or locally advanced prostate cancer undergoing definitive treatment.</p> <p>The secondary objectives include: description of the type of imaging modality used in the Brazilian setting to monitor BCR, the proportion of high-risk BCR patients, patients' baseline clinicopathological characteristics, time to BCR and time from BCR to initiation of first-line treatment post-BCR and the analysis of clinical and pathological variables associated with first-line treatment choice for these patients.</p> <p>The study also allows the exploration of the 10-year BCR rate in men and the treatment patterns post-BCR.</p>
Country(ies) of Study	Brazil
Number of Sites or Data Sources	1 site (Hospital Erasto Gaertner)

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Table of Contents

1	ABSTRACT	8
2	LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS	11
3	INVESTIGATORS	13
4	OTHER RESPONSIBLE PARTIES	13
5	MILESTONES	14
6	RATIONALE AND BACKGROUND	14
7	RESEARCH QUESTION AND OBJECTIVES	15
7.1	Research Question	15
7.2	Objectives	15
7.2.1	Primary Objective	15
7.2.2	Secondary Objectives	15
7.2.3	Exploratory Objectives	16
8	AMENDMENTS AND UPDATES TO THE PROTOCOL	16
9	RESEARCH METHODS	16
9.1	Study Design	16
9.1.1	Study Schematic	18
9.1.2	Endpoints	20
9.2	Setting	21
9.3	Patients	22
9.3.1	Inclusion Criteria	22
9.3.2	Exclusion Criteria	22
9.4	Variables	22
9.5	Data Sources and Measurement	23
9.6	Bias	23
9.7	Study Size	23
9.8	Data Transformation	23
9.9	Statistical Methods	23
9.9.1	Main Summary Measures	23
9.9.2	Statistical Methods Applied to the Study	24
9.9.3	Missing Values	26
9.9.4	Sensitivity Analyses	26

9.9.5	Changes to the Planned Analysis	26
9.10	Quality Control	26
10	RESULTS	27
10.1	Patients	27
10.2	Descriptive Data	28
10.3	Outcome Data	36
10.4	Main Results	46
10.5	Other Analyses	48
10.6	Adverse Events/Adverse Reactions	48
11	DISCUSSION	48
11.1	Key Results	48
11.2	Limitations	48
11.3	Interpretation	48
11.4	Generalizability	48
12	OTHER INFORMATION	48
13	CONCLUSIONS	48
14	REFERENCES	49
15	ANNEXES	50

List of In-text Tables

Table 1: Milestones	14
Table 2: Amendments and Updates to the Protocol	16
Table 3: Amendments to the Statistical Analysis Plan (SAP).....	26
Table 4: Sample Description	28
Table 5: Patient and disease characteristics of the 5-year BCR patients; non-5-year BCR patients; and the whole sample.	28
Table 6: Patient and disease characteristics of the 10-year BCR patients; non-10-year BCR patients; and the whole sample.	30
Table 7: Definitive treatment characteristics of the 5-year BCR patients; non-5-year BCR patients; and the whole sample.	31
Table 8: Definitive treatment characteristics of the 10-year BCR patients; non-10-year BCR patients; and the whole sample.	32
Table 9: Baseline clinicopathological characteristics in patients progressing to mHSPC (high and low volume) and nmHSPC (high and low risk) after definitive treatment.	33
Table 10: Patient and disease characteristics grouped by treatments.	35
Table 11: Post-definitive treatment information of the 5-year BCR patients; non-5-year BCR patients; and the whole sample.	36
Table 12: Post-definitive treatment information of the 10-year BCR patients; non-10-year BCR patients; and the whole sample.	37
Table 13: First-Line Treatment post-BCR Characteristics of the 5-year BCR patients; and the whole sample.	39
Table 14: First-Line Treatment post-BCR Characteristics of the 10-year BCR patients.	40
Table 15: First-Line Treatment post-BCR characteristics in patients progressing to mHSPC (high and low volume) and nmHSPC (high and low risk).	41
Table 16: Analysis of time-to-BCR for the nmHSPC patients.	44
Table 17: Analysis of time from BCR to first line treatment by risk status for patients who have had BCR.	44
Table 18: Association between type of treatment and clinical/pathological characteristics.	45

List of In-text Figures

Figure 1: Study Flow Chart	18
Figure 2A: Study Schema (overall study)	19
Figure 3B: Study Schema (Post-BCR analysis)	20
Figure 4: Kaplan-Meier plot of the time-to-BCR for low- vs high-risk patients (nmHSPC). a) time-to-5yr BCR; b) time-to-10yr BCR.	46
Figure 5: Kaplan-Meier plot of the time-to-BCR for low- vs high-volume patients (mHSPC). a) time-to-5yr BCR; a) time-to-10yr BCR.	Erro! Indicador não definido.
Figure 6: Kaplan-Meier plot of the time from BCR to initiation of first-line treatment for low- vs high-risk patients (nmHSPC).	47

Figure 7: Kaplan-Meier plot of the time from BCR to initiation of first-line treatment for
low- vs high-volume patients (mHSPC). **Erro! Indicador não definido.**

1 ABSTRACT

Title

Biochemical Recurrence following Prostate Cancer definitive treatment in Brazil: A Retrospective Chart Review Study

Keywords

Biochemical Recurrence, Prostate Cancer, PSA

Rationale and Background

Prostate Cancer (PCa) is the most prevalent cancer among men in Brazil, accounting for approximately 29% of all cancers in this population (INCA 2020)². Worldwide it is the second most common cancer among man (Sung et al. 2021)¹.

Despite achieving effective long-term cancer control, a significant proportion of men (ranging from 27% to 53%) who undergo radical prostatectomy (RP) or radiotherapy (RT) will experience biochemical recurrence (BCR) in 10 years. This is identified by an increase in serum Prostate-specific antigen (PSA) levels within 10 years after the primary definitive treatment (EUA Guidelines 2022; Freedland et al. 2005; Litwin and Tan 2017; Pound et al. 1999)⁴⁻⁶.

Since BCR is associated with increased morbidity and mortality related to the development of distant metastasis (EUA Guidelines 2022; Freedland et al. 2005)^{4,6}, determining the risk of disease progression in men with BCR is crucial. This study aimed at describing characteristics of disease recurrence after the PCa definitive treatment with curative intent in a Brazilian real-world setting.

Research Question and Objectives

To define the natural history of biochemical recurrence after primary definitive treatment in a Brazilian real-world setting, we aim to characterize the high-risk biochemical recurrence population after definitive treatment (radical prostatectomy or radiotherapy [including brachytherapy] ± hormone therapy, or both, with curative intent) in men with localized or locally advanced prostate cancer.

Primary Objective:

- To determine the 5-year BCR rate in men with localized or locally advanced prostate cancer undergoing definitive treatment.

Secondary Objectives:

- To describe the type of disease monitoring imaging modality used at BCR;
- To describe the proportion of non-metastatic (nmHSPC) and metastatic hormone sensitive prostate cancer (mHSPC) patients progressing from definitive treatment;
- To describe the proportion of high risk BCR patients (PSA doubling time < 10 months and ≤ 9 months);

- To evaluate baseline clinicopathological characteristics in patients progressing to mHSPC and nmHSPC after definitive treatment (overall population, high and low risk BCR);
- To describe time to BCR;
- To describe treatment pattern for first-line post-BCR;
- To describe time from BCR to initiation of first-line treatment;
- To analyze clinical and pathological variables associated with first-line treatment choice for post-BCR.

Exploratory Objectives:

- To determine the 10-year BCR rate in men with localized or locally advanced prostate cancer undergoing definitive treatment;
- To describe treatment pattern post-BCR according to metastatic and risk status (low and high risk BCR) and disease volume (high and low volume mHSPC, according to CHAARTED criteria).

Study Design

This is a retrospective, observational, medical chart cohort review. This study used data from electronic medical records of the Hospital Erasto Gaertner in Brazil. The hospital holds a Cancer Registry per type of cancer, which shows all patients seen at the institution, type of treatment employed and if they were followed at the institution or not. Patients undergoing definitive treatment for prostate cancer (radical prostatectomy or radiotherapy \pm hormone therapy, including brachytherapy, or both, with curative intent) between January 1st, 2005, and December 31st, 2018, have been selected through the database and their electronic medical charts were reviewed.

Setting

The single site, Hospital Erasto Gaertner, located in south region of Brazil, gathered data from the medical chart to the electronic Case Report File (eCRF) of 1003 patients. The data includes various variables, including demographic and clinical characteristics, definitive treatment information, PSA levels, monitoring imaging tests and post-BCR treatment details.

Patient and Study Size

Patients with confirmed adenocarcinoma of the prostate initially treated by RT or RP with curative intent were included. The study aimed to analyze the data of 1000 eligible patients; however, 1003 patients had the chart review performed and, of those, 10 cases were excluded due to screening failure or eCRF duplication.

Variables and Data Sources

The data was gathered from patients' electronic medical records from Hospital Erasto Gaertner. During the chart review, the variables of interest were collected: patient demographics, disease

characteristics, definitive treatment characteristics, pos-definitive treatment characteristics and first-line treatment post-BCR characteristics.

Results

Discussion and Conclusions

Marketing Authorization Holder(s)

Astellas Pharma Brazil

Name(s) and Affiliation(s) of Principal/Coordinating Investigator(s)

Dr. Murilo de Almeida Luz

Hospital Erasto Gaertner

2 LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

ADT	Androgen Deprivation Therapy
AUROC	Area Under the Receiver Operating Characteristics
BCR	Biochemical Recurrence
CRAs	Clinical Research Associates
CRO	Contract/Clinical Research Organization
CT	Computed Tomography
eCRF	electronic Case Report Form
EMR	Electronic Medical Record
FPI	First Patient In
IEC	Independent Ethics Committee
IQR	Interquartile Range
IRB	Institutional Review Board
ISUP	International Society of Urological Pathology
KM	Kaplan-Meier
LHRH	Luteinizing hormone-releasing hormone
LPI	Last Patient In
mHSPC	Metastatic Hormone Sensitive Prostate Cancer
MRI	Magnetic Resonance Imaging
N	Number
N/A	Not Applicable/Not Available
nmHSPC	Non-Metastatic Hormone Sensitive Prostate Cancer
PCa	Prostate Cancer
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PET/CT	Positron Emission Tomography/Computed Tomography Scan
PH	Proportional Hazards
PSA	Prostate-specific antigen
PSADT	PSA Doubling Time
RP	Radical Prostatectomy
RT	Radiotherapy
RTOG-ASTRO	Radiation Therapy Oncology Group – American Society for Radiation Oncology
SAP	Statistical Analysis Plan
SDV	Source Verification Data
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
T	Tumor

List of Terms

Baseline period	The allowable period of time preceding the index date for identifying chart data for abstraction.
Biochemical recurrence (BCR)	Defined as a rise in PSA to ≥ 2 ng/mL and a confirmatory value of 0.2 ng/mL or greater following radical prostatectomy, or a rise of 2 ng/mL or more above the nadir PSA after radiation therapy, according to PCWG3 criteria. Patients with persistent PSA post-PR are not considered BCR.
Definitive treatment for prostate cancer	Radical prostatectomy or radiotherapy (including brachytherapy) \pm hormone therapy, or both, with curative intent.
First-line of therapy post-BCR	The first treatment initiated following BCR identification within any given interval.
Follow-up period (also referred to as post-index period)	The period of time from the index date until last follow up or date of death.
High-risk BCR	Having BCR as described above plus PSADT ≤ 9 months or PSADT < 10 months.
High-volume mHSPC	Presence of visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis, according to CHAARTED criteria.
Index date	The date of the initiation of definitive treatment for prostate cancer

Index period	Spanning January 1st, 2005, to December 31st, 2018, the period containing allowable index dates for patients with charts eligible for data abstraction.
Metastatic hormone-sensitive prostate cancer (mHSPC)	Prostate cancer progressing from definitive treatment with detectable metastasis.
Persistent PSA after radical prostatectomy	Defined as detectable post-RP PSA of ≥ 0.1 ng/mL within 4 to 8 weeks of surgery.
PSADT	PSADT will be estimated based on the degree of change in PSA values over time and the number of months elapsing during the course of these changes.
Time from BCR to initiation of first-line treatment	The time interval (months) between the identification of BCR and the initiation of any treatment.
Time-to-BCR	The time interval (months) between definitive treatment and the identification of BCR.

3 INVESTIGATORS

Principal Investigator	Murilo de Almeida Luz
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4 OTHER RESPONSIBLE PARTIES

Contract Research Organization (CRO): Site Monitoring/Study Management	Oracle Life Sciences
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5 MILESTONES

Table 1: Milestones

Milestone (Brazil)	Planned Date	Actual Date	Comments
Start of data collection	26 Dec 2022	24 Feb 2023	FPI
End of data collection	23 Mar 2023	31 May 2023	LPI
End of first interim data collection	N/A	17 Mar 2023	A planned date was not set for the interim analysis since it was performed accordingly to when the study would have the greatest number of participants specifically to a congress submission in April 2023.
End of second interim data collection	N/A	13 Sep 2023	Not previously planned in the initial timeline.
First IRB/IEC approval	19 Dec 2022	13 Feb 2023	N/A
Last IRB/IEC approval	19 Dec 2022	13 Feb 2023	This is a one-site study.
Last Data Analysis and Statistical Analysis Report (first draft)	30 Mar 2023	03 Dec 2023	N/A
Clinical Study Report (final)	15 Sep 2023	TBC (29 Jan 2024)	N/A

6 RATIONALE AND BACKGROUND

Prostate cancer is the second most common cancer among men worldwide and the fifth leading cause of cancer death among men in 2020 (Sung et al. 2021)¹. In Brazil, it is the most prevalent cancer among men, accounting for 29.2% of all cancers in this population (INCA 2020)².

According to treatment guidelines and depending on several clinical and pathological factors such as pre-treatment PSA levels, radical prostatectomy (RP) and/or radiotherapy (RT) are recommended for clinically localized or locally advanced disease (EUA Guidelines 2022; Litwin and Tan 2017)^{3,4}. Despite excellent long-term cancer control, between 27% and 53% of all of men undergoing RP or RT will develop BCR, characterized by rising serum PSA levels within 10 years following primary definitive treatment (EUA Guidelines 2022; Freedland et al. 2005; Litwin and Tan 2017; Pound et al. 1999)³⁻⁶.

It is well-known that patients experiencing PSA-only recurrence after definitive treatment are at risk of developing distant metastases, PCa-related morbidity, and mortality. However, the effect size of BCR as a strong risk factor for mortality is highly variable and only specific patient subgroups with BCR might be at a higher risk of distant metastasis and mortality compared to many patients who develop a BCR and have an indolent disease clinical course (EUA Guidelines 2022; Freedland et al. 2005)^{4,6}.

Since BCR may be associated with increased need for secondary treatment, which can negatively impact quality of life, determining the risk of disease progression in men with BCR is crucial to guide physicians and patients to make informed decisions about the progression of the disease and need for treatment (EUA Guidelines 2022; Pound et al. 1999)4,5.

In order to determine the disease/condition according to its rarity/seriousness, this study provides information on the target population by categorizing BCR patients into high and low risk. In Brazil, very few data are available to support the characterization of the disease, the treatment approaches and the patient's clinical and pathological information.

7 RESEARCH QUESTION AND OBJECTIVES

7.1 Research Question

To define the natural history of biochemical recurrence after primary definitive treatment in a Brazilian real-world setting, we aim to characterize the high-risk biochemical recurrence population after definitive treatment (radical prostatectomy or radiotherapy [including brachytherapy] ± hormone therapy, or both, with curative intent) in men with localized or locally advanced prostate cancer.

The study design is a retrospective, observational, medical chart cohort review. This study used data from electronic medical records of the Hospital Erasto Gaertner, which is a public oncological reference center in Brazil. The hospital holds a Cancer Registry per type of cancer, which shows all patients seen at the institution, type of treatment employed and if they were followed at the institution or not. Patients undergoing definitive treatment for prostate cancer [radical prostatectomy or radiotherapy (including brachytherapy) ± hormone therapy, or both, with curative intent) between January 1st, 2005, and December 31st, 2018, have been selected through the database and their electronic medical charts were reviewed.

7.2 Objectives

7.2.1 Primary Objective

To determine the 5-year BCR rate in men with localized or locally advanced prostate cancer undergoing definitive treatment.

7.2.2 Secondary Objectives

- To describe the type of disease monitoring imaging technique at BCR (i.e., Computed Tomography (CT) scan, Magnetic Resonance Imaging (MRI), 68Ga-PSMA-PET/CT etc);
- To describe the proportion of non-metastatic (nmHSPC) and metastatic hormone sensitive prostate cancer (mHSPC) patients progressing from definitive treatment;
- To describe the proportion of high risk BCR patients (PSA doubling time < 10 months (Pound et al. 1999)5 and ≤ 9 months (Freedland et al. 2021)11);

- To evaluate baseline clinicopathological characteristics in patients progressing to mHSPC and nmHSPC after definitive treatment (overall population, high and low risk BCR);
- To describe time to BCR;
- To describe treatment pattern for first-line post-BCR (surveillance, ADT, local treatment and others);
- To describe time from BCR to initiation of first-line treatment;
- To analyze clinical and pathological variables (age at PCa diagnosis; surgical margin status; lymph node invasion; Gleason score; ISUP (International Society of Urological Pathology) grade; pathologic T stage, PSA-DT; pre-definitive treatment PSA; interval to biochemical failure, last PSA previous to post-BCR first-line treatment and last clinical staging previous to post-BCR first-line treatment) (EUA Guidelines 2022)⁴ associated with first-line treatment choice for post-BCR.

7.2.3 Exploratory Objectives

- To determine the 10-year BCR in men with localized or locally advanced prostate cancer undergoing definitive treatment;
- To describe treatment pattern post-BCR according to metastatic and risk status (low and high risk BCR) and disease volume (high and low volume mHSPC, according to CHAARTED criteria (Sweeney et al. 2015)¹³).

8 AMENDMENTS AND UPDATES TO THE PROTOCOL

Table 2: Amendments and Updates to the Protocol

Protocol Version	Date of Study Protocol	Section of Study Protocol	Amendment or Update	Reason
v2.0	10 May 2023	Sections 6.1 and 6.2	Substantial Amendment	Update on BCR definition and PSADT calculation

9 RESEARCH METHODS

9.1 Study Design

The study design is a retrospective, observational, medical record cohort review. This study used data from electronic medical records of the Hospital Erasto Gaertner, which is a public oncological reference center in Brazil. The hospital holds a Cancer Registry per type of cancer, which shows all patients seen at the institution, type of treatment employed and if they were followed at the institution or not. Patients undergoing definitive treatment for prostate cancer (radical prostatectomy or radiotherapy [including brachytherapy] \pm hormone therapy, or both, with curative intent) between January 1st, 2005, and December 31st, 2018, have been selected through the database and their electronic medical records were reviewed. Figure 1 shows the

study flow and possible evolution of the patient throughout the disease continuum after definitive treatment.

The index date 1 (for the primary endpoints and all the other endpoints before or at BCR) was considered the date of the initiation of definitive treatment. For patients undergoing RP this was the date of the surgery; for patients undergoing RT this was the date of the first session and for patients receiving combination treatment with hormone therapy, this was the date of the first treatment application (either hormone therapy or RT/RP). Patient and disease characteristics and treatment approach (curative and post-BCR) were retrospectively collected from medical records. The follow-up window spans from the index date to September-2022 (Figure 2A).

Biochemical recurrence was defined according to PCWG3 criteria (Scher et al. 2016)¹²: a rise in PSA to ≥ 2 ng/mL and a confirmatory value of 0.2 ng/mL or greater following radical prostatectomy, or a rise of 2 ng/mL or more above the nadir PSA after radiation therapy. PSA values and respective dates after definitive treatment were assessed to determine the lowest value (nadir) and eventual increases.

For patients undergoing radical prostatectomy a PSA of < 0.1 ng/mL within 4 to 8 weeks of surgery is needed in order to ensure that the identification of biochemical recurrence is accurate. A persistent PSA after radical prostatectomy is defined in the majority of studies as detectable post-RP PSA of ≥ 0.1 ng/mL within 4 to 8 weeks of surgery and it may result from persistent local disease, pre-existing metastasis, or residual benign prostate tissue (EUA Guidelines 2022)⁴. These patients were considered as “persistent PSA post-RP” and were not included in the BCR calculation and subsequent analyses.

For patients undergoing radiation therapy, PSA drops more slowly as compared to post radical prostatectomy. The interval before reaching the nadir can be up to 3 years, or more. At the 2006 RTOG-ASTRO Consensus Conference the Phoenix definition of radiation failure was proposed to establish a better correlation between definition and clinical outcome (mainly metastases), namely, an increase of 2 ng/mL above the post-treatment PSA nadir. This definition also applies to patients who received hormonal manipulation (EUA Guidelines 2022)⁴.

To define high risk BCR, the PSA doubling time (PSADT) was calculated considering at least 2 PSA measurements after BCR identification. Furthermore, all PSA measures that composed the PSADT calculation were collected up to the post-BCR treatment (if any post-BCR treatment is present).

The study started with prostate cancer patients undergoing definitive treatment. Based on PSA values and eventual rises, patients with BCR were identified, following definitions abovementioned. The occurrence of BCR was recorded to assess the rate of BCR within 5 and 10 years. The interval from definitive treatment to the occurrence of BCR was used to evaluate the time-to-BCR throughout the study period.

Out of all BCR patients, metastatic and non-metastatic patients were identified based on imaging results outlined in the charts. Post-definitive treatment nmHSPC (BCR) patients were

categorized as high and low risk, based on PSADT. Post-definitive treatment mHSPC patients were categorized as high and low volume, according to CHAARTED criteria (Sweeney et al. 2015)¹³. Baseline clinical and disease characteristics were described for the overall population and for the subgroups: BCR (low and high risk) and mHSPC (low and high volume).

First-line treatment post-BCR and respective time interval between BCR and initiation of treatment were assessed for the overall population and for each of those subgroups (see study flowchart; Figure 1). Baseline clinical and pathological variables and PSA and clinical staging before initiation of post-BCR treatment were analyzed to determine factors associated with post-BCR treatment choice. For these analyses a data index 2 was considered as the date of occurrence of BCR. To allow for a minimum period of treatment choice/initiation after BCR of 6 months, index date 2 was set at 31 March 2022 and the follow-up window for these assessments spanned through 30 September 2022 (Figure 2B).

9.1.1 Study Schematic

Figure 1: Study Flow Chart

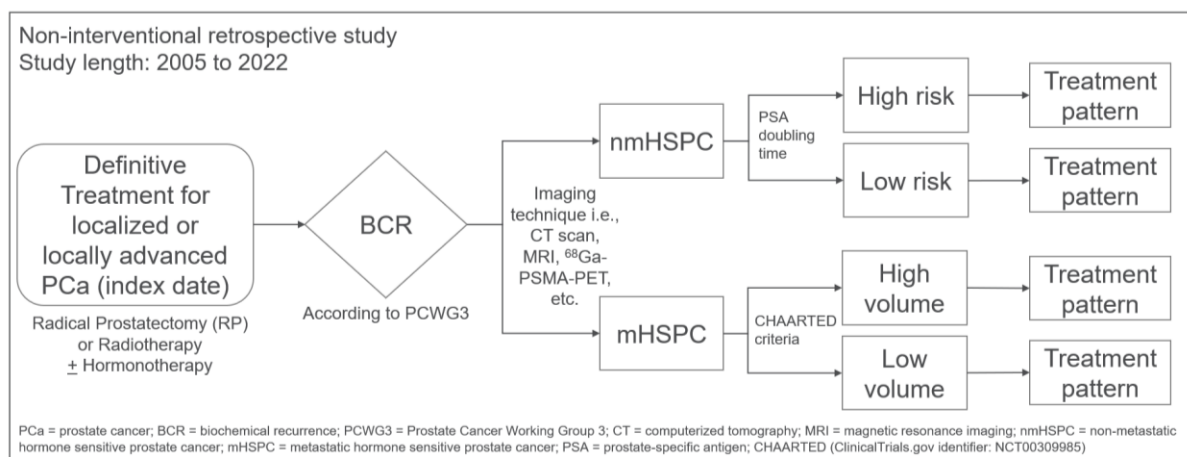
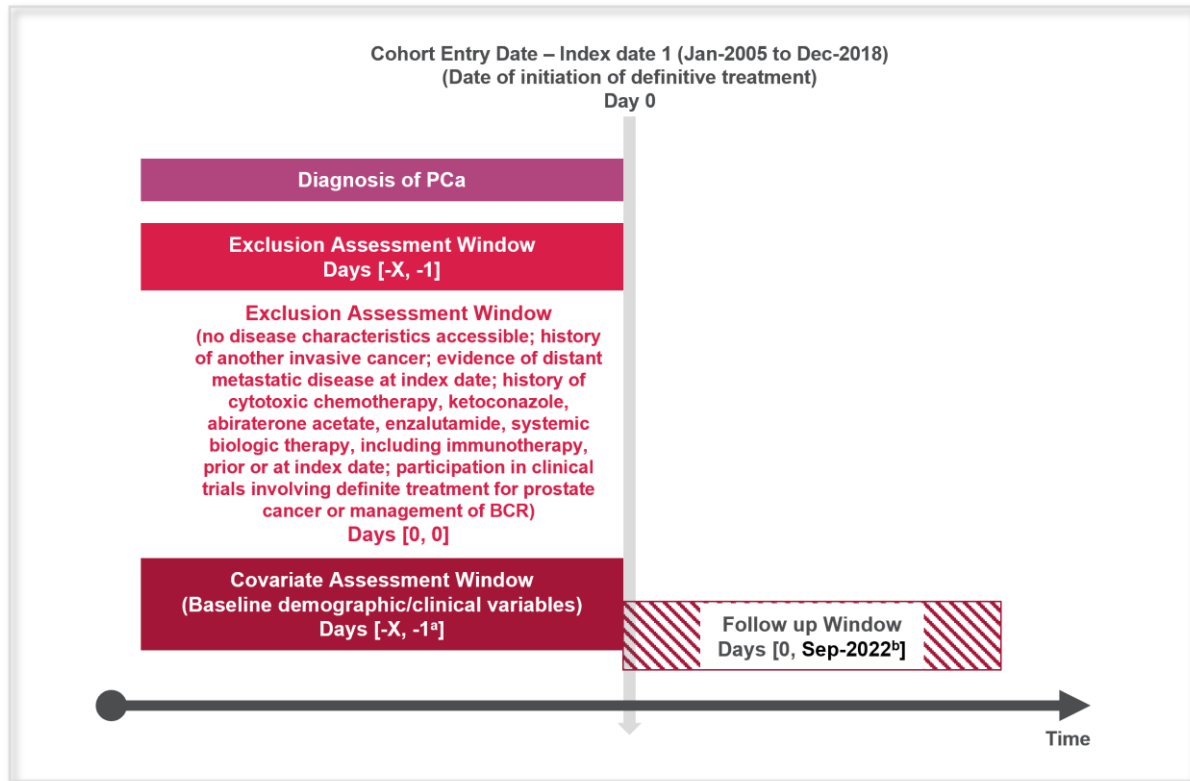
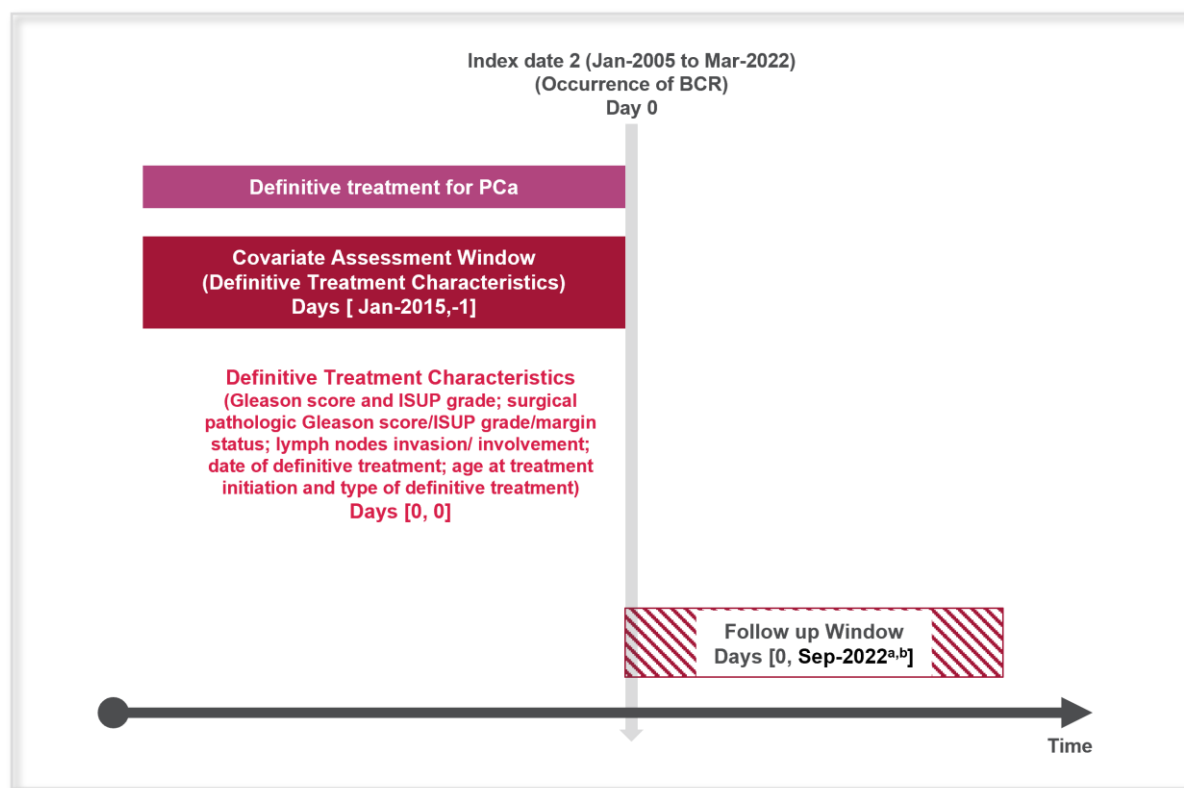


Figure 2A: Study Schema (overall study)



- a. Baseline demographic/clinical variables included: Year of birth, race; age at PCa diagnosis; region of residence; date of PCa diagnosis; clinical staging at diagnosis, pathologic T staging; PSA at diagnosis, pre-definitive treatment PSA; biopsy pathologic Gleason score and ISUP grade.
- b. Post-definitive treatment PSA measures - (1) To define post-curative treatment PSA nadir [lowest level identified] (2) To define BCR: PSA rise based on PCWG3 criteria (3) To define PSADT

Figure 3B: Study Schema (Post-BCR analysis)



- a. For post-BCR analysis a minimum time between BCR occurrence and last follow-up (variables collection) will be 6 months
b. Variables: type of disease monitoring imaging technique post-BCR; presence of metastasis post-BCR; site and number of metastasis post-BCR; first-line treatment post-BCR initiation date, last PSA previous to post-BCR first-line treatment and last clinical staging previous to post-BCR, type of first-line treatment post-BCR

9.1.2 Endpoints

Objectives	Endpoints
Primary	
To determine the 5-year BCR rate in men with localized or locally advanced prostate cancer undergoing definitive treatment	5-year BCR rate (according to PCWG3 (Scher et al. 2016) ¹²)
Secondary	
To describe the type of disease monitoring imaging at BCR i.e., CT scan, MRI, 68Ga-PSMA-PET, etc	Type of disease monitoring imaging modality at BCR, i.e., CT scan, MRI, 68Ga-PSMA-PET, etc
To describe the proportion of non-metastatic (nmHSPC) and metastatic hormone sensitive prostate cancer (mHSPC) patients progressing from definitive treatment	Proportion of non-metastatic (nmHSPC) and metastatic hormone sensitive prostate cancer (mHSPC) patients progressing from definitive treatment

Objectives	Endpoints
To describe the proportion of high risk BCR patients (PSA doubling time < 10 months and ≤ 9 months)	Proportion of high risk BCR patients (PSA doubling time < 10 months and ≤ 9 months)
To evaluate baseline clinicopathological characteristics in patients progressing to mHSPC and nmHSPC after definitive treatment (high and low risk)	Baseline clinicopathological characteristics in patients progressing to mHSPC and nmHSPC after definitive treatment (high and low risk)
To describe time to BCR	Time to BCR
To describe treatment pattern for first-line post-BCR (surveillance, ADT, local treatment and others)	First-line treatment regimens post-BCR (surveillance, ADT, local treatment) and their respective rates
To describe the time interval between BCR and initiation of first-line treatment	Time from BCR to initiation of first-line treatment
To analyze clinical and pathological variables (age at PCa diagnosis; surgical margin status; lymph node invasion; Gleason score; ISUP grade; pathologic T stage, PSADT; pre-definitive treatment PSA; interval to biochemical failure; last PSA previous to post-BCR first-line treatment and last clinical staging previous to post-BCR first-line treatment) (EUA Guidelines 2022) ⁴ associated with first-line treatment choice for post-BCR	Clinical and pathological variables (age at PCa diagnosis; surgical margin status; lymph node invasion; Gleason score; ISUP grade; pathologic T stage, PSA-DT; pre-definitive treatment PSA; interval to biochemical failure; last PSA previous to post-BCR first-line treatment and last clinical staging previous to post-BCR first-line treatment) (EUA Guidelines 2022) ⁴ associated first-line treatment choice for post-BCR
Exploratory	
To determine the 10-year BCR rate in men with localized or locally advanced prostate cancer undergoing definitive treatment	10-year BCR rate (according to PCWG3 (Scher et al. 2016) ¹² or defined by the investigator)
To describe treatment pattern post-BCR according to metastatic and risk status (low and high risk BCR) and disease volume (low and high volume mHSPC)	First-line treatment regimens post-BCR according to metastatic and risk status (low and high risk BCR) and disease volume (low and high volume mHSPC) and their respective rates

9.2 Setting

Upon the conclusion of the study, data was gathered through a medical record review for 1003 patients originating from the single participating site, Hospital Erasto Gaertner, situated in South Brazil. The compiled dataset encompassed various categories, including demographic and clinical characteristics, definitive treatment information, PSA levels, monitoring imaging

tests and post-BCR treatment details. This study was of a descriptive nature; hence, it did not incorporate any control or comparator groups.

The phase of data collection within Brazil took place between 24 February 2023 and 31 May 2023.

The participating Principal Investigator is a surgical oncologist for the last 15 years out of which 13 years of his experience has been in urological oncology field. The physician was instructed to follow the protocol details and the specific index dates determined for this study and evaluate all eligible and potential participants with the goal of minimizing potential selection bias. Furthermore, the physician was responsible for confirming patient eligibility as part of this process.

9.3 Patients

Prostate cancer patients ≥ 18 years old and above undergoing definitive treatment (radical prostatectomy or radiotherapy [including brachytherapy] \pm hormone therapy, or both, with curative intent) between January 1st, 2005, and December 31st, 2018, and followed up at Hospital Erasto Gaertner.

9.3.1 Inclusion Criteria

- Histologically or cytologically confirmed adenocarcinoma of the prostate at initial biopsy, without neuroendocrine differentiation, signet cell, or small cell features;
- Prostate cancer initially treated by radical prostatectomy or radiotherapy (including brachytherapy) \pm hormone therapy, or both, with curative intent.

9.3.2 Exclusion Criteria

- Patient with no disease characteristics accessible;
- History of another invasive cancer;
- Prior or present evidence of distant metastatic disease at index date as assessed by radiographic imaging;
- History of cytotoxic chemotherapy, ketoconazole, abiraterone acetate, enzalutamide, systemic biologic therapy, including immunotherapy, prior or at index date;
- Patients participating in clinical trials involving definite treatment for prostate cancer or management of BCR.

9.4 Variables

This study assessed the variables as described below:

- **Patient Demographics:** year of birth, race, age at PCa diagnosis and region of residence.
- **Disease Characteristics:** Date of PCa diagnosis, clinical staging at diagnosis, pathologic T staging, PSA at diagnosis, pre-definitive treatment PSA, biopsy

pathologic Gleason score, biopsy ISUP grade, surgical pathologic Gleason score, surgical margin status, surgical ISUP grade, lymph nodes invasion/involvement.

- **Definitive Treatment Characteristics:** date of definitive treatment, age at treatment initiation, type of definitive treatment.
- **Pos-definitive treatment Characteristics:** post-definitive treatment PSA measures, date of BCR, type of disease monitoring imaging technique post-BCR, PSADT post-BCR, presence of metastasis post-BCR.
- **First-Line Treatment post-BCR Characteristics:** date of first-line treatment post-BCR initiation, PSA level, clinical staging, type of first-line treatment post-BCR.

9.5 Data Sources and Measurement

Participant's medical records from Hospital Erasto Gaertner were used as data source. All medical charts are electronic and an electronic Case Report File (eCRF) was used to record the data (refer to Annex 1 regarding last version and date of the document).

9.6 Bias

Some representativeness bias in this study was present due to limitations of the sample, as it included only those who were treated in the Hospital Erasto Gaertner, and it encompassed patients who had exclusively undergone a definitive treatment with curative intent.

Data was not collected from patients treated by non-participating physicians and the patients were selected in the south region in Brazil, where the hospital is located, potentially introducing a selection bias.

9.7 Study Size

Originally, the study had planned the involvement of only one site in the south region of the country and the inclusion of 1000 patients. However, the single site was able to proceed with the inclusion of a total of 1003 patients, of those, 10 patients were excluded from the analysis: 4 patients due to screening failure and 6 due to eCRF duplication.

9.8 Data Transformation

All detailed methodology for data transformations is documented in the Statistical Analysis Plan (SAP).

9.9 Statistical Methods

The detailed statistical methodology utilized for the study is in the SAP (refer to Annex 1 regarding last version and date of the document).

9.9.1 Main Summary Measures

All analyses were conducted descriptively, and as a result, all employed methods were aligned with this descriptive nature. All study measures are summarized descriptively through tabular and graphical displays. The technique employed depended on the variable type. The section 9.9.2 and SAP has details about the measures used (Annex X).

9.9.2 Statistical Methods Applied to the Study

This study is a descriptive analysis of retrospective patient-level data. Results are reported in aggregate. The specific method used depends on the type of variable as described below:

Categorical variables – described using:

- Number of observations (n)
- Number and percent (%) within each category
- Number of missing observations

Numeric variables – described using:

- Number of observations (n)
- Mean & Standard deviation
- Minimum and maximum
- Median and interquartile range (IQR)
- 95% confidence intervals
- Number of missing observations

All endpoints were calculated for the overall population and by the stratification presented in this document (minimum of 50 patients per subgroup). The proportion of patients with BCR within 5- and 10-years post-index are presented as a percentage of the patients undergoing definite treatment and by type of treatment (i.e., radical prostatectomy or radiation therapy).

All clinical, and demographic variables are summarized by absolute and relative frequencies (categorical variables) and by measures such as mean, standard deviation, median and interquartile range (IQR) (continuous variables). Data may be further stratified according to any characteristics of interest available in the database. The choice of mean or median was performed according to data distribution, for skewed data, the median was preferred.

Time-to-event analyses (time-to-BCR and time from BCR to initiation of first-line treatment) were calculated and analyzed using the Kaplan-Meier (KM) method to allow for right-censoring. Deaths and loss of follow-up were censored. Exploratory comparisons in time from BCR to initiation of first-line treatment analyses across subgroups (low- and high-risk BCR and low and high-volume mHSPC patients) were made by log-rank tests. Corresponding Kaplan-Meier curves were generated as appropriate. Survival point estimates and 95% confidence intervals were provided at predetermined time points of interest every year.

An adjusted analysis, to analyze clinical and pathological variables (age at PCa diagnosis; surgical margin status; lymph node invasion; Gleason score; ISUP grade; pathologic T stage, PSA-DT; pre-definitive treatment PSA; interval to biochemical failure; last PSA previous to post-BCR first-line treatment and last clinical staging previous to post-BCR first-line treatment) (EUA Guidelines 2022)¹¹ associated with first-line treatment choice, were performed by fitting a multivariable regression model (e.g., multinomial logistic regression

model, Cox proportional hazard model). Measures of the association were presented as (adjusted) odds ratio by fitting the multinomial logistic regression with the choice of first line treatment as a response variable and the clinical and pathological variables as covariate. To fit the model, the first line treatment was categorized into three types:

- No treatment (surveillance)
- Local treatment (RT, RP)
- Systemic treatment, including:
 - ADT (orchiectomy, LHRH agonist or antagonist)
 - ADT + 1st generation antiandrogen (> 2 weeks [Bicalutamide; Flutamide or Nilutamide/cyproterone acetate; megestrol acetate; medroxyprogesterone acetate])
 - ADT + chemotherapy
 - ADT + new hormonal agents [Apalutamide; Darolutamide; Enzalutamide or Abiraterone]

In cases where the parameters were not estimable due to convergence issue, appropriate remedial methods were investigated and applied. The complete selection of model started with the predictor with the highest area under the receiver operating characteristics (AUROC) to predict 5-year BCR. Subsequently, the rest of the variables were introduced one by one, creating all the possible models of two independent variables, and the combination of higher AUROC will be chosen. A logistic regression was performed as a multivariable analysis to be used in the AUROC. This process was repeated to form models of 3, 4 and more variables, always choosing the combination with the highest AUROC. The process was stopped when the inclusion of a new variable in the model means an increase lower than 0.005 units in the AUROC.

The association between time-to-BCR and clinical and pathological variables measured before BCR were analyzed by fitting Cox proportional hazards (PH) models using the high/low risk patients as a subgroup for investigation. Additionally, the high/low volume mHSPC patients were considered as another subgroup for investigation. The resulting hazard ratio and 95% confidence interval were included in the summary. Censoring assumptions followed the same rules as applied for the KM estimates; i.e., patients who died or lost follow up were censored at the time first known to be dead or lost follow up. The proportional hazards assumption was tested based on graphical examination of KM curves, to confirm they do not cross and by Schoenfeld test. If the proportional hazards assumption was violated, appropriate remedial methods were further investigated and applied. The same analysis was repeated using time-to-5-year BCR, time-to-10-year BCR, and time-to-first line treatment use (calculated from BCR) as a response variable in the Cox PH model.

Death was not expected in this stage due to PCa, so we didn't anticipate a large number of deaths. The number of death events was checked, analyzed, and reported. Patients moving out (referrals to other institutions) was also not expected, due to the nature of the public health

system in Brazil. Nevertheless, the proportion of patients without required follow-up was checked, analyzed, and reported as well. In cases where of zero patients died or lost follow up, the Cox PH model was not appropriate, and thus additional remedy was investigated and applied.

Data analyses were performed by Cerner Enviza, an Oracle Company, in accordance with Cerner Enviza's standard operating procedures (SOPs) for statistics and clinical programming. All study-specific processes and definitions were documented. The statistical analysis was coordinated by the responsible biostatistician of Cerner Enviza. Any changes from the analyses after conducting any of the analyses outlined in the SAP was captured as a revision to the SAP and documented in the study report. All analyses and figures were conducted using R (version 4.2.0) and Python (version 3.10.6).

9.9.3 Missing Values

Missing and unknown categories for each variable were presented. Percentages were calculated excluding missing values. Subjects with missing values for an endpoint did not contribute to the analysis of that endpoint.

9.9.4 Sensitivity Analyses

To explore the possible effect of sample losses due to deaths or other reasons, we performed a worst-case scenario analysis and compared it with available case analysis. The sensitivity analysis was performed regarding time to BCR survival analysis. We assumed that all patients who died or did not continue the study survived in their respective groups, then, we compared these results to the available analysis.

9.9.5 Changes to the Planned Analysis

The study SAP went through an amendment.

Table 3: Amendments to the Statistical Analysis Plan (SAP)

SAP Version	Date of Study SAP	Section of Study SAP	Amendment or Update	Reason
V3.0	10 May 2023	Sections 6.1 and 6.2	Substantial Amendment	Update on BCR definition and PSADT calculation

9.10 Quality Control

Steps were taken to ensure to highest quality to data and process during the study.

The single site Principal Investigator and the site staff were remotely trained regarding the Site Initiation Visit (SIV). This training covered a diversity of aspects of the study including the study protocol, procedures, eCRF training, eligibility criteria, data entry, adverse event, study timeline and regulatory obligations.

Cerner Enviza periodically followed up with the site to ensure the processes were being followed and mitigation measures were being taken to avoid screening failure and duplicate entries due to the high number of participants that was planned to be included.

Monitoring visits were excluded from the study process; however, a Source Verification Data (SDV) was performed to ensure data quality of 50 randomly selected participants.

The electronic Case Report Form (eCRF) included automated queries. The data management team and Clinical Research Associates (CRAs) could generate manual queries if confirmation or clarification was needed.

10 RESULTS

10.1 Patients

A total of 1003 patients were included in the study, of which 10 cases were excluded. The exclusions were attributed to the following reasons: four cases were excluded due to patient ineligibility (screening failure) and six cases were excluded due to a duplicate entry.

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10.2 Descriptive Data

Sample Description

Out of the total sample of 1003 eligible patients in the study, 32 patients were excluded cases, of which 22 were due to discrepancies between PSA values and collection dates and 10 due to screening failure or data duplication. Yet, 96.81% of the whole sample was analyzed to achieve the study objectives.

Table 4: Sample Description

Variable	Sample (N=1003) n (%)
Number of patients analyzed	971 (96.81)
Number of patients with BCR (1)	193 (19.24)
Number of patients with BCR within 5 years	131 (67.88)
Number of patients with BCR after 5 years	62 (32.12)
Number of patients with BCR within 10 years	184 (95.33)
Number of patients with BCR after 10 years	9 (4.67)
Number of patients with nmHSPC	96 (9.57)
Number of patients with mHSPC post definitive treatment	39 (3.89)
Number of deaths	0 (0.00)
Number of excluded cases (2)	10 (1.00)
Number of excluded patients due to discrepancies in PSA values or collection dates (3)	22 (2.19)

(1) The proportion of patients 5-year BCR, 10-year BCR, after 5- and 10 year is in respect to the BCR sample.

(2) Out of 1003 patients included in the study, 10 patients were excluded from the whole sample: four patients were excluded due to screening failure and the remaining 6 patients were excluded due to duplication of their data.

(3) Twenty-two patients were excluded due to discrepancies between PSA values and collection dates; specifically, the number of PSA values did not match the PSA collection date. This exclusion resulted from instances where either the date or values were missing.

Patient Demographics and Disease Characteristics

The table 5 regarding 5-year and non-5-year BCR patients among the whole sample presents the demographics and disease characteristics. The mean age of 5-year BCR patients at data gathering was 64.93 ± 7.83 years while for non-5-year BCR patients was 64.41 ± 7.57 years. The clinical stage for both groups and the whole sample was mainly identified to be unclassified. Regarding the ISUP grade of diagnostic biopsy, most 5-year BCR patients were classified between ISUP 1 (31.3%) and ISUP 2 (28.24%).

Table 5: Patient and disease characteristics of the 5-year BCR patients; non-5-year BCR patients; and the whole sample.

Category	Variables	5-year BCR patients (N=131)	non-5-year BCR patients (N=840)	Whole sample (N=971)
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Patient Characteristics	Age	Mean ± std Median [IQR] Range	Patient's age at PCa diagnosis (years)	64.93 ± 7.83 65.00 [60.00, 71.00] 45.00 – 82.00	64.41 ± 7.57 65.00 [59.00, 69.00] 41.00 – 83.00	64.48 ± 7.60 65.00 [59.00, 70.00] 41.00 – 83.00
	Race	n (%)	Asian (yellow) Black Brown Caucasian (white) Other	0 (0.00) 8 (6.11) 6 (4.58) 117 (89.31) 0 (0.00)	4 (0.48) 42 (5.00) 33 (3.93) 759 (90.36) 2 (0.24)	4 (0.41) 50 (5.15) 39 (4.02) 876 (90.22) 2 (0.21)
	Region	n (%)	South Southeast Midwest North North East	131 (100.00) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00)	840 (100.00) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00)	971 (100.00) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00)
Disease Characteristics	PSA (at diagnosis)	Mean ± std Median [IQR] Range	PSA level (ng/mL)	21.98 ± 27.56 12.95 [7.83, 24.85] 1.50 – 215.00	13.74 ± 16.53 9.00 [5.90, 14.90] 0.00 – 151.60	14.90 ± 18.67 9.30 [6.00, 15.95] 0.00 – 215.00
	Clinical stage at diagnosis	n (%)	I IIA IIB IIC IIIA IIIB IIIC IVA Unclassified	0 (0.00) 4 (3.05) 1 (0.76) 3 (2.29) 0 (0.00) 0 (0.00) 1 (0.76) 4 (3.05) 118 (90.08)	10 (1.19) 40 (4.76) 0 (0.00) 0 (0.00) 2 (0.24) 7 (0.83) 8 (0.95) 12 (1.43) 761 (90.60)	10 (1.03) 44 (4.53) 1 (0.10) 3 (0.31) 2 (0.21) 7 (0.72) 9 (0.93) 16 (1.65) 879 (90.53)
	Clinical staging primary tumor (T)	n (%)	Tx T1 T1a T1b T1c T2 T2a T2b T2c T3 T3a T3b T4 Unknown	67 (51.15) 0 (0.00) 0 (0.00) 1 (0.76) 1 (0.76) 7 (5.34) 3 (2.29) 2 (1.53) 18 (13.74) 1 (0.76) 7 (5.34) 12 (9.16) 1 (0.76) 11 (8.40)	479 (57.02) 3 (0.36) 3 (0.36) 2 (0.24) 15 (1.79) 10 (1.19) 40 (4.76) 29 (3.45) 144 (17.14) 11 (1.31) 33 (3.93) 34 (4.05) 5 (0.60) 32 (3.81)	546 (56.23) 3 (0.31) 3 (0.31) 3 (0.31) 16 (1.65) 17 (1.75) 43 (4.43) 31 (3.19) 162 (16.68) 12 (1.24) 40 (4.12) 46 (4.74) 6 (0.62) 43 (4.43)
	Clinical staging regional lymph nodes (N)	n (%)	Nx N0 N1 Unknown	77 (58.78) 32 (24.43) 4 (3.05) 18 (13.74)	600 (71.43) 185 (22.02) 14 (1.67) 41 (4.88)	677 (69.73) 217 (22.35) 18 (1.85) 59 (6.08)
	Clinical staging distant metastasis (M)	n (%)	Mx M0 M1 M1a M1b M1c Unknown	31 (23.66) 90 (68.70) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00) 10 (7.63)	421 (50.12) 384 (45.71) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00) 35 (4.17)	452 (46.55) 474 (48.82) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00) 45 (4.63)
	Biopsy Gleason – 1st degree	n (%)	1 2 3 4 5	0 (0.00) 1 (0.76) 77 (58.78) 49 (37.40) 4 (3.05)	0 (0.00) 9 (1.07) 645 (76.79) 174 (20.71) 12 (1.43)	0 (0.00) 10 (1.03) 722 (74.36) 223 (22.97) 16 (1.65)
	Biopsy Gleason – 2nd degree	n (%)	1 2 3	0 (0.00) 1 (0.76) 59 (45.04)	0 (0.00) 10 (1.19) 566 (67.38)	0 (0.00) 11 (1.13) 625 (64.37)

	Biopsy ISUP grade	n (%)	4	65 (49.62)	234 (27.86)	299 (30.79)
			5	6 (4.58)	30 (3.57)	36 (3.71)
			1 (Gleason 2-6)	41 (31.30)	480 (57.14)	521 (53.66)
			2 (Gleason 7 (3+4))	37 (28.24)	174 (20.71)	211 (21.73)
			3 (Gleason 7 (4+3))	19 (14.50)	93 (11.07)	112 (11.53)
			4 (Gleason 8)	24 (18.32)	59 (7.02)	83 (8.55)
			5 (Gleason 9-10)	10 (7.63)	34 (4.05)	44 (4.53)

Regarding the BCR calculation, one year was calculated as days/365.25 rounded up to 1 significant digit.

Table 6 provides the descriptions of the 10-year and non-10-year BCR patients among the whole sample. Regarding these patients, the mean age of the 10-year BCR patients was 65.13 ± 7.85 , while for non-10-year BCR patients was 64.33 ± 7.54 years. The mean PSA level at diagnosis for the 10-year BCR patients was of 20.67 ± 26.72 .

Table 6: Patient and disease characteristics of the 10-year BCR patients; non-10-year BCR patients; and the whole sample.

Category	Variables			10-year BCR patients (N=184)	non-10-year BCR patients (N=787)	Whole sample (N=971)
Patient Demographics	Age	Mean \pm std Median [IQR] Range	Patient's age at PCa diagnosis (years)	65.13 ± 7.85 66.00 [60.00, 71.00] 45.00 – 82.00	64.33 ± 7.54 65.00 [59.00, 69.00] 41.00 – 83.00	64.48 ± 7.60 65.00 [59.00, 70.00] 41.00 – 83.00
	Race	n (%)	Asian (yellow) Black Brown Caucasian (white) Other	0 (0.00) 9 (4.89) 7 (3.80) 167 (90.76) 1 (0.54)	4 (0.51) 41 (5.21) 32 (4.07) 709 (90.09) 1 (0.13)	4 (0.41) 50 (5.15) 39 (4.02) 876 (90.22) 2 (0.21)
	PSA (at diagnosis)	Mean \pm std Median [IQR] Range	PSA level (ng/mL)	20.67 ± 26.72 12.25 [7.55, 22.15] 1.50 – 215.00	13.50 ± 15.84 8.90 [5.80, 14.70] 0.00 – 141.00	14.90 ± 18.67 9.30 [6.00, 15.95] 0.00 – 215.00
	Clinical stage at diagnosis	n (%)	I IIA IIB IIC IIIA IIIB IIIC IVA Unknown	0 (0.00) 5 (2.72) 1 (0.54) 3 (1.63) 0 (0.00) 0 (0.00) 1 (0.54) 6 (3.26) 168 (91.30)	10 (1.27) 39 (4.96) 0 (0.00) 0 (0.00) 2 (0.25) 7 (0.89) 8 (1.02) 10 (1.27) 711 (90.34)	10 (1.03) 44 (4.53) 1 (0.10) 3 (0.31) 2 (0.21) 7 (0.72) 9 (0.93) 16 (1.65) 879 (90.53)
	Clinical staging primary tumor (T)	n (%)	Tx T0 T1 T1a T1b T1c T2 T2a T2b T2c T3 T3a T3b T4 Unknown	99 (53.80) 0 (0.00) 0 (0.00) 0 (0.00) 1 (0.54) 2 (1.08) 7 (3.80) 5 (2.72) 3 (1.63) 26 (14.13) 2 (1.09) 7 (3.80) 15 (8.15) 2 (1.09) 15 (8.15)	447 (56.80) 0 (0.00) 3 (0.38) 3 (0.38) 2 (0.25) 14 (1.79) 10 (1.27) 38 (4.83) 28 (3.56) 136 (17.28) 10 (1.27) 33 (4.19) 31 (3.94) 4 (0.51) 28 (3.56)	546 (56.23) 0 (0.00) 3 (0.31) 3 (0.31) 3 (0.31) 16 (1.65) 17 (1.75) 43 (4.43) 31 (3.19) 162 (16.68) 12 (1.24) 40 (4.12) 46 (4.74) 6 (0.62) 43 (4.43)
Disease Characteristics			Nx	115 (62.50)	562 (71.41)	677 (69.73)

	Clinical staging regional lymph nodes (N)	n (%)	N0	40 (21.74)	177 (22.49)	217 (22.35)
			N1	6 (3.26)	12 (1.53)	18 (1.85)
			Unknown	23 (12.50)	36 (4.57)	59 (6.08)
	Clinical staging distant metastasis (M)	n (%)	Mx	55 (29.35)	397 (50.57)	452 (46.55)
			M0	115 (62.50)	359 (45.61)	474 (48.82)
			M1	0 (0.00)	0 (0.00)	0 (0.00)
			M1a	0 (0.00)	0 (0.00)	0 (0.00)
			M1b	0 (0.00)	0 (0.00)	0 (0.00)
			M1c	0 (0.00)	0 (0.00)	0 (0.00)
			Unknown	15 (8.15)	30 (3.81)	45 (4.63)
	Biopsy Gleason – 1st degree	n (%)	1	0 (0.00)	0 (0.00)	0 (0.00)
			2	1 (0.54)	9 (1.14)	10 (1.03)
			3	112 (60.87)	610 (77.51)	722 (74.36)
			4	66 (35.87)	157 (19.95)	223 (22.97)
			5	5 (2.72)	11 (1.40)	16 (1.65)
	Biopsy Gleason – 2nd degree	n (%)	1	0 (0.00)	0 (0.00)	0 (0.00)
			2	1 (0.54)	10 (1.27)	11 (1.13)
			3	92 (50.00)	533 (67.73)	625 (64.37)
			4	83 (45.1)	216 (27.45)	299 (30.79)
			5	8 (4.35)	28 (3.56)	36 (3.71)
	Biopsy ISUP grade	n (%)	1 (Gleason 2-6)	64 (34.78)	457 (58.07)	521 (53.66)
			2 (Gleason 7 (3+4))	49 (26.63)	162 (20.58)	211 (21.73)
			3 (Gleason 7 (4+3))	29 (15.76)	83 (10.55)	112 (11.53)
			4 (Gleason 8)	30 (16.30)	53 (6.73)	83 (8.55)
			5 (Gleason 9-10)	12 (6.52)	32 (4.07)	44 (4.53)

Regarding the BCR calculation, one year was calculated as days/365.25 rounded up to 1 significant digit.

Definitive Treatment Characteristics

Table 7 display the characteristics of the definitive treatment PCa patients underwent with curative intent. The data collected in the CRF showed the majority of 5-year BCR patients were submitted to RP (36,64%) or RT (25.19%), however, there is also a portion of patients in the group that undergo RP plus RT treatment. Among the whole sample, RP was the most common definitive treatment.

Table 7: Definitive treatment characteristics of the 5-year BCR patients; non-5-year BCR patients; and the whole sample.

Category	Variables			5-year BCR patients (N=131)	non-5-year BCR patients (N=840)	Whole sample (N=971)
Definitive Treatment Characteristics	PSA level before definitive treatment.	Mean ± std Median [IQR] Range	PSA level (ng/mL)	23.20 ± 30.85 12.9 [7.80, 26.00] 1.00 – 215.00	13.85 ± 16.91 8.90 [5.60, 14.90] 0.10 – 151.60	15.17 ± 19.75 9.30 [5.90, 15.85] 0.10 - 215.00
	Age at treatment initiation	Mean ± std Median [IQR] Range	Patient's age (years)	65.20 ± 7.65 65.00 [60.00, 71.00] 45.00 – 82.00	64.55 ± 7.58 65.00 [59.00, 70.00] 41.00 – 87.00	64.64 ± 7.58 65.00 [60.00, 70.00] 41.00 – 87.00
	Type of definitive treatment	n (%)	RP	48 (36.64)	487 (57.98)	535 (55.10)
			RP + Neoadjuvant HT	1 (0.76)	3 (0.36)	4 (0.41)
			RP + Adjuvant HT	1 (0.76)	3 (0.36)	4 (0.41)
			RP + RT (including brachytherapy)	25 (19.08)	110 (13.10)	135 (13.90)
			RP + RT + Neoadjuvant HT	2 (1.53)	8 (0.95)	10 (1.03)
			RP + RT + Adjuvant HT	4 (3.05)	9 (1.07)	13 (1.34)
			RT (including brachytherapy)	33 (25.19)	172 (20.48)	205 (21.11)

			RT (including brachytherapy) + Neoadjuvant HT	8 (6.11)	19 (2.26)	27 (2.78)
			RT (including brachytherapy) + Adjuvant HT	9 (6.87)	27 (3.21)	36 (3.71)
			Other	0 (0.00)	2 (0.24)	2 (0.21)
	RP patients	n		81	620	701
	Surgical ISUP grade (for RP patients)	n (%)	1 (Gleason 2-6)	13 (16.05)	232 (37.42)	245 (34.95)
			2 (Gleason 7 (3+4))	25 (30.86)	200 (32.26)	225 (32.10)
			3 (Gleason 7 (4+3))	18 (22.22)	98 (15.81)	116 (16.55)
			4 (Gleason 8)	13 (16.05)	40 (6.45)	53 (7.56)
			5 (Gleason 9-10)	12 (14.81)	50 (8.06)	62 (8.85)
	Radiotherapy dosage (only for RT patients)	n (%)	(grays)	71.63 ± 6.63 70.00 [70.00, 76.00] 38.00 – 77.00	70.77 ± 12.07 72.00 [70.00, 76.00] 12.00 – 175.00	70.94 ± 11.23 72.00 [70.00, 76.00] 12.00 – 175.00
	Pathologic T staging (for RP patients)	n (%)	T0	0 (0.00)	1 (0.16)	1 (0.10)
			Tx	5 (6.17)	54 (8.71)	59 (6.08)
			Tis	0 (0.00)	3 (0.48)	3 (0.31)
			T1	1 (1.23)	8 (1.29)	9 (0.93)
			T2	45 (55.56)	391 (63.06)	436 (44.90)
			T3	30 (37.04)	161 (25.97)	191 (19.67)
			T4	0 (0.00)	2 (0.32)	2 (0.20)
	Biopsy Gleason - first degree of the surgical piece (for RP patients)		1	0 (0.00)	2 (0.32)	2 (0.29)
			2	0 (0.00)	5 (0.81)	5 (0.71)
			3	39 (48.15)	430 (69.35)	469 (66.90)
			4	35 (43.21)	169 (27.26)	204 (29.10)
			5	7 (8.64)	14 (2.26)	21 (3.00)
	Biopsy Gleason - second degree of the surgical piece (for RP patients)	n (%)	1	0 (0.00)	2 (0.32)	2 (0.29)
			2	1 (1.23)	3 (0.48)	4 (0.57)
			3	31 (38.27)	327 (52.74)	358 (51.07)
			4	41 (50.62)	244 (39.35)	285 (40.66)
			5	8 (9.88)	44 (7.10)	52 (7.42)
	Surgical margin (for RP patients)	n (%)	Positive	47 (58.02)	211 (34.03)	258 (36.80)
			Negative	32 (39.51)	397 (64.03)	429 (51.20)
			Unknown	2 (2.47)	12 (1.94)	14 (2.00)
	Lymph nodes involvement (for RP patients)	n (%)	Yes	5 (6.17)	23 (3.71)	28 (3.99)
			No	54 (66.67)	475 (76.61)	529 (75.46)
			Unknown	22 (27.16)	122 (19.68)	144 (20.54)

Regarding the BCR calculation, one year was calculated as days/365.25 rounded up to 1 significant digit. The proportion of patients in the Surgical ISUP grade is in respect to the RP number of patients and not the whole sample.

Regarding 10-year-BCR and non-10-year BCR, the table 8 shows the definitive treatment characteristics for both groups and the whole sample. 10-year-BCR patients also were mainly submitted to RP (34.24%) or RT (25.54%) or both RP plus RT definitive treatments combined (20.11%).

Representing only 0.82% of the whole sample, the less common treatment PCa patients underwent was RP combined with adjuvant or neoadjuvant hormone therapy.

Table 8: Definitive treatment characteristics of the 10-year BCR patients; non-10-year BCR patients; and the whole sample.

Category	Variables			10-year BCR patients (N=184)	non-10-year BCR patients (N=787)	Whole sample (N=971)
Definitive Treatment Characteristics	PSA level before definitive treatment.	Mean ± std Median [IQR] Range	PSA level (ng/mL)	21.47 ± 29.22	13.63 ± 16.28	15.17 ± 19.75
				12.10 [7.48, 22.85]	8.90 [5.60, 14.73]	9.30 [5.90, 15.85]
				1.0 – 215.00	0.10 - 141.00	0.10 - 215.00

	Age at treatment initiation	Mean ± std Median [IQR] Range	Patient's age (years)	65.31 ± 7.61 66.00 [60.00, 71.00] 45.00 – 82.00	64.48 ± 7.57 65.00 [59.00, 69.50] 41.00 – 87.00	64.64 ± 7.58 65.00 [60.00, 70.00] 41.00 – 87.00
	Type of definitive treatment	n (%)	RP	63 (34.24)	472 (59.97)	535 (55.10)
			RP + Neoadjuvant HT	1 (0.54)	3 (0.38)	4 (0.41)
			RP + Adjuvant HT	1 (0.54)	3 (0.38)	4 (0.41)
			RP + RT (including brachytherapy)	37 (20.11)	98 (12.45)	135 (13.90)
			RP + RT + Neoadjuvant HT	3 (1.63)	7 (0.89)	10 (1.03)
			RP + RT + Adjuvant HT	5 (2.72)	8 (1.02)	13 (1.34)
			RT (including brachytherapy)	47 (25.54)	158 (20.08)	205 (21.11)
			RT (including brachytherapy) + Neoadjuvant HT	10 (5.44)	17 (2.16)	27 (2.78)
			RT (including brachytherapy) + Adjuvant HT	17 (9.24)	19 (2.41)	36 (3.71)
			Other	0 (0.00)	2 (0.25)	2 (0.21)
	RP patients	n		110	591	701
	Surgical ISUP grade (for RP patients)	n (%)	1 (Gleason 2-6)	18 (16.36)	227 (38.41)	245 (34.95)
			2 (Gleason 7 (3+4))	35 (31.82)	190 (32.15)	225 (32.10)
			3 (Gleason 7 (4+3))	25 (22.73)	91 (15.40)	116 (16.55)
			4 (Gleason 8)	17 (15.45)	36 (6.09)	53 (7.56)
			5 (Gleason 9-10)	15 (13.64)	47 (7.95)	62 (8.84)
	Radiotherapy dosage (only for RT patients)	Mean ± std Median [IQR] Range	(grays)	72.06 ± 5.78 72.00 [70.00, 76.00] 38.00 – 78.00	70.48 ± 12.77 72.00 [70.00, 76.00] 12.00 – 175.00	70.93 ± 11.23 72.00 [70.00, 76.00] 12.00 – 175.00
	Pathologic T staging (for RP patients)	n (%)	T0	0 (0.00)	1 (0.17)	1 (0.14)
			Tx	8 (7.27)	51 (8.63)	59 (8.42)
			Tis	0 (0.00)	3 (0.51)	3 (0.42)
			T1	1 (0.91)	8 (1.35)	9 (1.28)
			T2	60 (54.55)	376 (63.62)	436 (62.20)
			T3	41 (37.27)	150 (25.38)	191 (27.25)
			T4	0 (0.00)	2 (0.34)	2 (0.29)
	Biopsy Gleason - first degree of the surgical piece (for RP patients)	n (%)	1	0 (0.00)	2 (0.34)	2 (0.29)
			2	0 (0.00)	5 (0.85)	5 (0.71)
			3	55 (50.00)	414 (70.05)	469 (66.90)
			4	48 (43.64)	156 (26.40)	204 (29.10)
			5	7 (6.36)	14 (2.37)	21 (3.00)
	Biopsy Gleason - second degree of the surgical piece (for RP patients)	n (%)	1	0 (0.00)	2 (0.34)	2 (0.29)
			2	1 (0.91)	3 (0.51)	4 (0.57)
			3	43 (39.09)	315 (53.30)	358 (51.07)
			4	54 (49.09)	231 (39.09)	285 (40.66)
			5	12 (10.91)	40 (6.77)	52 (7.42)
	Surgical margin (for RP patients)	n (%)	Positive	60 (54.55)	198 (33.50)	258 (36.80)
			Negative	46 (41.82)	383 (64.81)	429 (61.20)
			Unknown	4 (3.64)	10 (1.69)	14 (2.00)
	Lymph nodes involvement (for RP patients)	n (%)	Yes	7 (6.36)	21 (3.55)	28 (3.99)
			No	73 (66.36)	456 (77.16)	529 (75.46)
			Unknown	30 (27.27)	114 (19.29)	144 (20.54)

Regarding the BCR calculation, one year will be calculated as days/365.25 rounded up to 1 significant digit. The proportion of patients in the Surgical ISUP grade is in respect to the RP number of patients and not the whole sample.

Table 9: Baseline clinicopathological characteristics in patients progressing to mHSPC (high and low volume) and nmHSPC (high and low risk) after definitive treatment.

Category	Variables	mHSPC			nmHSPC		
		High volume (N=5)	Low volume (N=30)	Whole sample (N=39)	High risk (N=35)	Low risk (N=50)	Whole sample (N=96)

Patient Characteristics	Age	Patient's age at PCa diagnosis (years)	71.4 ± 4.98 70.00 [68.00, 75.00] 66.00 – 78.00	63.17 ± 8.95 62.50 [57.00, 70.50] 47.00 – 82.00	64.49 ± 8.82 64 [57.50, 71.50] 47.00 – 82.00	65.88 ± 7.85 67.00 [61.50, 72.00] 45.00 – 76.00	63.64 ± 6.39 62.00 [60.00, 68.75] 50.00 – 76.00	64.85 ± 7.27 65.50 [60.00, 71.00] 45.00 – 80.00
	Race	Asian (yellow)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		Black	0 (0.00)	1 (3.33)	1 (2.56)	4 (9.68)	3 (5.88)	7 (7.29)
		Brown	0 (0.00)	3 (10.00)	3 (7.69)	1 (0.00)	1 (1.96)	2 (2.08)
		Caucasian (white)	5 (100.00)	26 (86.66)	35 (89.74)	30 (90.32)	46 (92.16)	87 (90.63)
		Other	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Disease Characteristics	PSA (at diagnosis)	PSA level (ng/mL)	48.02 ± 59.03 24 [14.5, 40.00] 10.00 – 151.60	15.89 ± 15.41 11.40 [6.90, 18.95] 1.60 – 77.00	20.05 ± 26.05 12.20 [7.00, 24.45] 1.60 – 151.60	16.45 ± 17.65 10.05 [7.20, 18.50] 4.60 – 96.00	23.79 ± 22.80 14.85 [8.80, 29.08] 3.20 – 100.00	19.70 ± 20.04 12.55 [7.43, 22.15] 2.60 – 100.00
	Clinical stage at diagnosis	I	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		IIA	0 (0.00)	1 (3.33)	1 (2.56)	0 (0.00)	2 (4.00)	2 (2.08)
		IIB	0 (0.00)	1 (3.33)	1 (2.56)	0 (0.00)	0 (0.00)	0 (0.00)
		IIC	0 (0.00)	0 (0.00)	0 (0.00)	2 (5.71)	1 (2.00)	3 (3.13)
		III	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		IIIA	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		IIIB	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		IIIC	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		IVA	0 (0.00)	1 (3.33)	1 (2.56)	3 (8.57)	1 (2.00)	4 (4.17)
		Unknown	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		Unclassified	5 (100.00)	27 (90.00)	36 (92.31)	30 (85.71)	46 (92.00)	87 (90.63)
	Clinical staging primary tumor (T)	Tx	4 (80.00)	16 (53.33)	23 (58.97)	18 (51.43)	34 (68.00)	58 (60.42)
		T0	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		T1	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		T1a	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		T1b	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.86)	0 (0.00)	1 (1.04)
		T1c	0 (0.00)	1 (3.33)	2 (5.13)	0 (0.00)	0 (0.00)	0 (0.00)
		T2	0 (0.00)	1 (3.33)	1 (2.56)	2 (5.71)	3 (6.00)	5 (5.21)
		T2a	0 (0.00)	1 (3.33)	1 (2.56)	1 (2.86)	1 (2.00)	2 (2.08)
		T2b	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.00)	1 (1.04)
		T2c	0 (0.00)	6 (20.00)	6 (15.38)	5 (14.29)	3 (6.00)	10 (10.42)
		T3	1 (20.00)	0 (0.00)	1 (2.56)	0 (0.00)	0 (0.00)	0 (0.00)
		T3a	0 (0.00)	2 (6.67)	2 (5.13)	0 (0.00)	2 (4.00)	3 (3.13)
		T3b	0 (0.00)	2 (6.67)	2 (5.13)	6 (17.14)	0 (0.00)	7 (7.29)
		T4	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		Unknown	0 (0.00)	1 (3.33)	1 (2.56)	2 (5.71)	6 (12.00)	9 (9.38)
	Clinical staging regional lymph nodes (N)	Nx	5 (100.00)	21 (70.00)	29 (74.36)	19 (54.29)	35 (70.00)	60 (62.50)
		N0	0 (0.00)	7 (23.33)	8 (20.51)	7 (20.00)	7 (14.00)	16 (16.67)
		N1	0 (0.00)	1 (3.33)	1 (2.56)	3 (8.57)	1 (2.00)	4 (4.17)
		Unknown	0 (0.00)	1 (3.33)	1 (2.56)	6 (17.14)	7 (14.00)	16 (16.67)
	Clinical staging distant metastasis (M)	Mx	0 (0.00)	5 (16.67)	8 (20.51)	11 (31.43)	19 (38.00)	35 (36.46)
		M0	5 (100.00)	25 (83.33)	31 (79.49)	22 (62.86)	25 (50.00)	52 (54.17)
		M1	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		M1a	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		M1b	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		M1c	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		Unknown	0 (0.00)	0 (0.00)	0 (0.00)	2 (5.71)	6 (12.00)	9 (9.38)
	Biopsy Gleason - 1° degree	1	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		2	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		3	1 (20.00)	0 (0.00)	19 (48.72)	19 (54.29)	33 (66.00)	62 (64.58)
		4	2 (40.00)	16 (53.33)	18 (46.15)	14 (40.00)	16 (32.00)	31 (32.29)
		5	2 (40.00)	14 (46.67)	2 (5.13)	2 (5.71)	1 (2.00)	3 (3.13)
	Biopsy Gleason - 2° degree	1	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		2	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		3	0 (0.00)	10 (33.33)	10 (25.64)	22 (62.86)	35 (70.00)	62 (64.58)
		4	3 (60.00)	17 (56.67)	24 (61.54)	13 (37.14)	14 (28.00)	33 (34.38)
		5	2 (40.00)	3 (10.00)	5 (12.82)	0 (0.00)	1 (2.00)	1 (1.04)

Biopsy ISUP grade	1 (Gleason 2-6)	0 (0.00)	6 (20.00)	6 (15.38)	15 (42.86)	23 (46.00)	43 (44.79)
	2 (Gleason 7 (3+4))	1 (20.00)	10 (33.33)	13 (33.33)	4 (11.43)	10 (20.00)	19 (19.79)
	3 (Gleason 7 (4+3))	0 (0.00)	4 (13.33)	4 (10.26)	7 (20.00)	12 (24.00)	19 (19.79)
	4 (Gleason 8)	1 (20.00)	7 (23.33)	10 (25.64)	7 (20.00)	3 (6.00)	11 (11.46)
	5 (Gleason 9-10)	3 (60.00)	3 (10.00)	6 (15.38)	2 (5.71)	2 (4.00)	4 (4.17)

Regarding the BCR calculation, one year was calculated as days/365.25 rounded up to 1 significant digit.

Table 10: Patient and disease characteristics grouped by treatments.

Category	Variables			No treatment (N=23)	Local treatment (N=201)	Systemic treatment (N=104)
Patient Characteristics	Age	Mean ± std Median [IQR] Range	Patient's age at PCa diagnosis (years)	70.00 ± 8.02 71.00 [66.00, 77.5] 47.00 – 80.00	62.97 ± 6.77 63.00 [59.00, 68.00] 41.00 – 80.00	67.11 ± 8.16 68.00 [61.75, 73.00] 44.00 – 82.00
	Race	n (%)	Asian (yellow) Black Brown Caucasian (white) Other	0 (0.00) 2 (8.69) 1 (4.35) 20 (86.96) 0 (0.00)	1 (0.50) 7 (3.48) 6 (2.99) 186 (92.54) 1 (0.50)	0 (0.00) 7 (6.73) 4 (3.85) 92 (88.46) 1 (0.96)
	PSA (at diagnosis)	Mean ± std Median [IQR] Range	PSA level (ng/mL)	21.51 ± 20.72 16.05 [8.97, 25.6] 4.90 – 99.00	13.07 ± 11.19 9.45 [6.50, 14.4] 1.50 – 78.00	26.68 ± 32.74 15.05 [8.75, 32.00] 0.20 – 215.00
	Clinical stage at diagnosis	n (%)	I II IIA IIB IIC IIIA IIIB IIIC IVA Unknown	0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00) 23 (100.00)	0 (0.00) 0 (0.00) 6 (2.99) 0 (0.00) 2 (1.00) 1 (0.49) 1 (0.49) 3 (1.49) 6 (2.99) 182 (90.55)	0 (0.00) 0 (0.00) 2 (1.92) 1 (0.96) 1 (0.96) 0 (0.00) 0 (0.00) 1 (0.96) 7 (6.73) 92 (88.46)
	Clinical staging primary tumor (T)	n (%)	Tx T0 T1 T1a T1b T1c T2 T2a T2b T2c T3 T3a T3b T4 Unknown	19 (82.61) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00) 1 (4.35) 0 (0.00) 0 (0.00) 1 (4.35) 0 (0.00) 0 (0.00) 0 (0.00) 1 (4.35) 0 (0.00) 1 (4.35)	89 (44.28) 0 (0.00) 0 (0.00) 0 (0.00) 1 (0.50) 2 (0.99) 6 (2.98) 7 (3.48) 6 (2.98) 40 (19.90) 2 (0.99) 16 (7.96) 18 (8.96) 1 (0.50) 13 (6.47)	71 (68.27) 0 (0.00) 0 (0.00) 0 (0.00) 1 (0.96) 1 (0.96) 2 (1.92) 1 (0.96) 0 (0.00) 8 (7.69) 2 (1.92) 4 (3.85) 11 (10.58) 1 (0.96) 2 (1.92)
Disease Characteristics	Clinical staging regional lymph nodes (N)	n (%)	Nx N0 N1 Unknown	20 (86.96) 2 (8.70) 0 (0.00) 1 (4.35)	120 (59.70) 52 (25.87) 6 (2.98) 23 (11.44)	76 (73.08) 16 (15.40) 7 (6.73) 5 (4.80)
	Clinical staging distant metastasis (M)	n (%)	Mx M0 M1 M1a M1b M1c Unknown	12 (52.17) 10 (43.48) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00) 1 (4.35)	84 (41.79) 104 (51.74) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00) 13 (6.46)	28 (26.92) 75 (72.11) 0 (0.00) 0 (0.00) 0 (0.00) 0 (0.00) 1 (0.96)

	Biopsy Gleason - 1° degree	n (%)	1	0 (0.00)	0 (0.00)	0 (0.00)
			2	0 (0.00)	3 (1.49)	0 (0.00)
			3	17 (73.91)	132 (65.67)	53 (50.96)
			4	5 (21.74)	59 (29.35)	46 (44.23)
			5	1 (4.35)	7 (3.48)	5 (4.8)
	Biopsy Gleason - 2° degree	n (%)	1	0 (0.00)	0 (0.00)	0 (0.00)
			2	1 (4.35)	1 (0.50)	0 (0.00)
			3	13 (56.52)	121 (60.20)	39 (37.50)
			4	9 (39.13)	73 (36.32)	55 (52.88)
			5	0 (0.00)	6 (2.98)	10 (9.62)
	Biopsy ISUP grade	n (%)	1 (Gleason 2-6)	11 (47.83)	91 (45.27)	19 (18.27)
			2 (Gleason 7 (3+4))	6 (26.09)	44 (21.89)	34 (32.69)
			3 (Gleason 7 (4+3))	2 (8.70)	30 (14.93)	20 (19.23)
			4 (Gleason 8)	4 (17.39)	26 (12.94)	18 (17.31)
			5 (Gleason 9-10)	0 (0.00)	10 (4.98)	13 (12.50)

Regarding the BCR calculation, one year was calculated as days/365.25 rounded up to 1 significant digit. No treatment: surveillance; Local treatment: RT and/or RP; Systemic treatment includes: ADT (orchiectomy, LHRH agonist or antagonist); TPA + 1st generation antiandrogen (> 2 weeks [Bicalutamide; Flutamide or Nilutamide/cyproterone acetate; megestrol acetate; medroxyprogesterone acetate]); TPA + chemotherapy; TPA + new hormonal agents [Apalutamide; Darolutamide; Enzalutamide or Abiraterone.

10.3 Outcome Data

Post-definitive Treatment Characteristics

Table 11: Post-definitive treatment information of the 5-year BCR patients; non-5-year BCR patients; and the whole sample.

Category	Variables			5-year BCR patients (N=131)	non-5-year BCR patients (N=840)	Whole sample (N=971)
Post-definitive treatment information	PSA values post-definitive treatment	Mean ± std Median [IQR] Range	PSA level (ng/mL). More than one exam can be added	Mean ± std Median [IQR] Range	Mean ± std Median [IQR] Range	Mean ± std Median [IQR] Range
	Type of imaging post definitive treatment	n (%)	CT Scan	40 (30.53)	8 (0.95)	48 (4.94)
			MRI	12 (9.16)	9 (1.07)	21 (2.16)
			68Ga-PSMA-PET	9 (6.87)	5 (0.59)	14 (1.44)
			Bone Scintigraphy	27 (20.61)	10 (1.19)	37 (3.81)
			Other	11 (8.40)	4 (0.48)	15 (1.55)
			Unclassified	32 (24.43)	804 (95.71)	836 (86.10)
	Metastasis post definitive treatment	n (%)	Yes	33 (25.19)	48 (5.71)	81 (8.34)
			No	75 (57.25)	315 (37.50)	390 (40.16)
			Unclassified	23 (17.56)	477 (56.79)	500 (51.49)
	AXIAL SKELETON (skull, rib cage, and spine) metastasis? (Only for patients with "Presence of metastasis post definitive treatment" marked as Yes.)	n (%)		16 (48.48)	24 (50.00)	40 (49.38)
	APPENDICULAR SKELETON metastasis (bones of the upper and lower limbs)? (Only for patients with "Presence of metastasis post	n (%)		8 (24.24)	14 (29.17)	22 (27.16)

	definitive treatment” marked as Yes.)					
	Number of bone metastases identified post definitive treatment	Mean ± std Median [IQR] Range	(Total number of both bone metastasis)	3.18 ± 2.18 2.00 [1.00, 6.00] 1.00 – 6.00	2.80 ± 2.78 1.00 [1.00, 3.00] 1.00 – 10.00	2.95 ± 2.54 2.00 [1.00, 4.75] 1.00 – 10.00
	Persistent PSA	n (%)		0 (0.00)	0 (0.00)	0 (0.00)
	Nadir	Mean ± std Median [IQR] Range	PSA level (ng/mL)	2.58 ± 13.77 0.00 [0.00, 0.65] 0.00 – 147.00	0.38 ± 0.95 0.00 [0.00, 0.30] 0.00 – 5.90	1.87 ± 11.39 0.00 [0.00, 0.50] 0.00 – 147.00
	PSADT	Mean ± std Median [IQR] Range	months	15.53 ± 28.14 8.14 [4.19, 13.99] 0.97 – 201.57	24.69 ± 23.07 18.27 [9.07, 29.26] 2.66 – 100.16	18.43 ± 26.89 10.60 [4.87, 19.95] 0.97 – 201.57
	Biochemical recurrence without metastasis	n (%)		69 (52.67)	27 (3.21)	96 (9.88)
	Biochemical recurrence with metastasis	n (%)		30 (22.90)	9 (1.07)	39 (4.02)
	Unclassified	n (%)		32 (24.43)	804 (95.71)	836 (86.10)
	PSADT > 9 months	n (%)		56 (42.75)	38 (4.52)	94 (9.68)
	PSADT ≤ 9 months	n (%)		52 (39.69)	11 (1.31)	63 (6.49)
	PSADT - negative	n (%)		15 (11.45)	6 (0.71)	21 (2.16)
	PSADT - non-calculable	n (%)		8 (6.11)	7 (0.83)	15 (1.55)
	PSADT - NA	n (%)		0 (0.00)	778 (92.62)	778 (80.12)
	PSADT > 10 months	n (%)		52 (39.69)	37 (4.40)	89 (9.17)
	PSADT ≤ 10 months	n (%)		56 (42.75)	12 (1.43)	68 (7.00)
	PSADT - negative	n (%)		15 (11.45)	6 (0.71)	21 (2.16)
	PSADT - non-calculable	n (%)		8 (6.11)	7 (0.83)	15 (80.12)
	PSADT - NA	n (%)		0 (0.00)	778 (92.62)	778 (80.12)
	Low-volume mHSPC	n (%)		23 (17.56)	7 (0.83)	30 (3.09)
	High-volume mHSPC	n (%)		4 (3.05)	1 (0.12)	5 (0.52)

Regarding the BCR calculation, one year was calculated as days/365.25 rounded up to 1 significant digit. One month was calculated as days/30.475 rounded up to 1 significant digit. The proportion of patients in the AXIAL and APPENDICULAR skeleton metastasis variable lines is in respect to the metastatic sample and not the whole sample. “PSADT - non-calculable” refers to patients with fewer than two measurements, making it impossible to calculate the PSADT value. “PSADT- NA” designates patients who did not experience biochemical recurrence, so the PSADT value was not calculated. The imaging exam data presented here pertains to either the first examination that collected metastatic data after definitive treatment or the initial exam post-definitive treatment for non-metastatic patients.

Table 12: Post-definitive treatment information of the 10-year BCR patients; non-10-year BCR patients; and the whole sample.

Category	Variables			10-year BCR patients (N=184)	non-10-year BCR patients (N=787)	Whole sample (N=971)
Post-definitive treatment information	PSA values post-definitive treatment	Mean ± std Median [IQR] Range	PSA level (ng/mL). More than one exam can be added.	Mean ± std Median [IQR] Range	Mean ± std Median [IQR] Range	Mean ± std Median [IQR] Range
	Type of imaging post definitive treatment	n (%)	CT Scan	46 (25.00)	2 (0.25)	48 (4.94)
			MRI	20 (10.87)	1 (0.13)	21 (2.16)
			68Ga-PSMA-PET	13 (7.07)	1 (0.13)	14 (1.44)

		Bone Scintigraphy	37 (20.11)	0 (0.00)	37 (3.81)
		Other	15 (8.15)	0 (0.00)	15 (1.55)
		Unclassified	53 (28.80)	783 (99.49)	836 (86.10)
Metastasis post definitive treatment	n (%)	Yes	45 (24.46)	36 (4.57)	81 (8.34)
		No	107 (58.15)	283 (35.96)	390 (40.16)
		Unknown	32 (17.39)	468 (59.47)	500 (51.49)
AXIAL SKELETON (skull, rib cage, and spine) metastasis? (Only for patients with "Presence of metastasis post definitive treatment" marked as Yes.)	n (%)		23 (51.11)	17 (47.22)	40 (49.38)
APPENDICULAR SKELETON metastasis (bones of the upper and lower limbs)? (Only for patients with "Presence of metastasis post definitive treatment" marked as Yes.)	n (%)		11 (24.44)	11 (30.55)	22 (27.16)
Number of bone metastases identified	Mean ± std Median [IQR] Range	(total number of both bone metastasis)	3.50 ± 2.52 2.50 [1.00, 6.00] 1.00 - 9.00	2.35 ± 2.48 1.00 [1.00, 3.00] 1.00 - 10.00	2.95 ± 2.54 2.00 [1.00, 4.75] 1.00 - 10.00
Persistent PSA			0 (0.00)	0 (0.00)	0 (0.00)
Nadir	Mean ± std Median [IQR] Range	PSA level (ng/mL)	1.94 ± 11.66 0.00 [0.00, 0.60] 0.00 - 147.00	0.39 ± 1.09 0.00 [0.00, 0.00] 0.00 - 3.30	1.87 ± 11.39 0.00 [0.00, 0.50] 0.00 - 147.00
PSADT	Mean ± std Median [IQR] Range	months	18.19 ± 27.19 9.32 [4.80, 18.96] 0.97 - 201.57	26.34 ± 12.52 24.76 [20.54, 30.57] 12.85 - 42.99	18.43 ± 26.90 10.60 [4.87, 19.95] 0.97 - 201.57
Biochemical recurrence without metastasis	n (%)		93 (50.54)	3 (0.38)	96 (9.89)
Biochemical recurrence with metastasis	n (%)		38 (20.65)	1 (0.13)	39 (4.02)
Biochemical recurrence - Unclassified	n (%)		53 (28.80)	783 (99.49)	836 (86.09)
PSADT > 9 months	n (%)		89 (48.37)	5 (0.64)	94 (9.68)
PSADT ≤ 9 months	n (%)		63 (34.23)	0 (0.00)	63 (6.49)
PSADT - negative	n (%)		18 (9.78)	3 (0.38)	21 (2.16)
PSADT - non-calculable	n (%)		14 (7.61)	1 (0.13)	15 (1.55)
PSADT - NA	n (%)		0 (0.00)	778 (98.86)	778 (80.12)
PSADT > 10 months	n (%)		84 (45.65)	5 (0.64)	89 (9.17)
PSADT ≤ 10 months	n (%)		68 (36.96)	0 (0.00)	68 (7.00)
PSADT - negative	n (%)		18 (9.78)	3 (0.38)	21 (2.16)
PSADT - non-calculable	n (%)		14 (7.61)	1 (0.13)	15 (1.54)
NA	n (%)		0 (0.00)	778 (98.86)	778 (80.12)
Low-volume mHSPC	n (%)		29 (15.76)	1 (0.13)	30 (3.09)
High-volume mHSPC	n (%)		5 (2.72)	0 (0.00)	5 (0.51)

Regarding the BCR calculation, one year was calculated as days/365.25 rounded up to 1 significant digit. One month was calculated as days/30.475 rounded up to 1 significant digit. The proportion of patients in the AXIAL and APPENDICULAR skeleton metastasis variable lines is in respect to the metastatic sample and not the whole sample. "PSADT - non-calculable" refers to patients with fewer than two measurements, making it impossible to calculate the PSADT value. "PSADT- NA" designates patients who did not experience biochemical recurrence, so the PSADT value was not calculated. The imaging exam data presented here pertains to either the first

examination that collected metastatic data after definitive treatment or the initial exam post-definitive treatment for non-metastatic patients.

First-Line Treatment post-BCR Characteristics

Table 13: First-Line Treatment post-BCR Characteristics of the 5-year BCR patients; and the whole sample.

Category	Variables			5-year BCR patients (N=131)	Whole sample (N=193)
First-Line Treatment post-BCR Characteristics	Clinical stage before initiation 1st-line treatment post-BCR	n (%)	I	n (% of population)	n (% of population)
			II	n (% of population)	n (% of population)
			III	n (% of population)	n (% of population)
			IV	n (% of population)	n (% of population)
			Unknown	n (% of population)	n (% of population)
	Clinical staging primary tumor (T)	n (%)	Tx	50 (38.17)	68 (35.23)
			T0	0 (0.00)	0 (0.00)
			T1	0 (0.00)	0 (0.00)
			T1a	0 (0.00)	0 (0.00)
			T1b	1 (0.76)	1 (0.52)
			T1c	0 (0.00)	1 (0.52)
			T2	10 (7.63)	12 (6.22)
			T2a	0 (0.00)	0 (0.00)
			T2b	5 (3.82)	7 (3.63)
			T2c	19 (14.50)	25 (12.95)
			T3	10 (7.64)	13 (6.74)
			T3a	9 (6.87)	15 (7.77)
			T3b	7 (5.34)	9 (4.66)
			T4	0 (0.00)	2 (1.04)
			Unknown	0 (0.00)	0 (0.00)
			Unclassified	20 (15.27)	40 (20.73)
	Clinical staging regional lymph nodes (N)		Nx	58 (44.27)	83 (43.01)
			N0	34 (25.95)	45 (23.32)

		n (%)	N1	14 (10.69)	18 (9.33)
			Unknown	5 (3.82)	7 (3.63)
			Unclassified	20 (15.27)	40 (20.73)
	Clinical staging distant metastasis (M)	n (%)	Mx;	57 (43.51)	89 (46.11)
			M0	39 (29.77)	43 (22.28)
			M1	13 (9.92)	18 (9.33)
			M1a	0 (0.00)	0 (0.00)
			M1b	1 (0.76)	1 (0.52)
			M1c	0 (0.00)	1 (0.52)
			Unknown	1 (0.76)	1 (0.52)
			Unclassified	20 (15.27)	40 (20.73)
	Type of treatment	n (%)	1 - Surveillance (no treatment)	4 (3.05)	14 (7.25)
			2 - Androgen Deprivation Therapy (TPA or ADT) [orchiectomy; LHRH agonist or antagonist]	50 (38.17)	65 (33.68)
			3 - TPA + 1st generation antiandrogen (> 2 weeks [Bicalutamide; Flutamide or Nilutamide/cyproterone acetate; megestrol acetate; medroxyprogesterone acetate]);	0 (0.00)	0 (0.00)
			4 - TPA + chemotherapy	0 (0.00)	1 (0.52)
			5 - TPA + new hormonal agents (NHT) [Apalutamide; Darolutamide; Enzalutamide or Abiraterone]	0 (0.00)	0 (0.00)
			6 - local treatment [PR; RT]	54 (41.22)	70 (36.27)
			7 - Other	2 (1.53)	2 (1.04)
			8 - Unclassified	21 (16.03)	41 (21.24)
	Time interval between BCR and initiation of 1st line of treatment post-BCR	n (%)	months	32.96 ± 14.40 31.89 [20.90, 45.68] 5.78 – 58.34	51.91 ± 33.10 44.73 [26.15, 69.24] 5.78 – 169.71

Since it is post BCR, the whole means patients with BCR within 5 years + patients with BCR after 5 years. Regarding the BCR calculation, one year was calculated as days/365.25 rounded up to 1 significant digit. One month was calculated as days/30.475 rounded up to 1 significant digit.

Table 14: First-Line Treatment post-BCR Characteristics of the 10-year BCR patients.

Category	Variables			10-year BCR patients (N=184)	Whole sample (N=193)
First-Line Treatment post-BCR Characteristics	Clinical stage before initiation 1st-line treatment post-BCR	n (%)	I	n (% of population)	n (% of population)
		n (%)	II	n (% of population)	n (% of population)
		n (%)	III	n (% of population)	n (% of population)
		n (%)	IV	n (% of population)	n (% of population)
		n (%)	Unknown	n (% of population)	n (% of population)
	Clinical staging primary tumor (T)	n (%)	Tx	65 (35.33)	68 (35.23)
		n (%)	T0	0 (0.00)	0 (0.00)
		n (%)	T1	0 (0.00)	0 (0.00)
		n (%)	T1a	0 (0.00)	0 (0.00)
		n (%)	T1b	1 (0.54)	1 (0.52)
		n (%)	T1c	1 (0.54)	1 (0.52)

		n (%)	T2	12 (6.52)	12 (6.22)
		n (%)	T2a	0 (0.00)	0 (0.00)
		n (%)	T2b	7 (3.80)	7 (3.63)
		n (%)	T2c	25 (13.59)	25 (12.95)
		n (%)	T3	12 (6.52)	13 (6.74)
		n (%)	T3a	12 (6.52)	15 (7.77)
		n (%)	T3b	9 (4.89)	9 (4.66)
		n (%)	T4	2 (1.09)	2 (1.04)
		n (%)	Unknown	0 (0.00)	0 (0.00)
		n (%)	Unclassified	38 (20.65)	40 (20.73)
		n (%)			
	Clinical staging regional lymph nodes (N)	n (%)	Nx	79 (42.93)	83 (43.01)
		n (%)	N0	42 (22.83)	45 (23.32)
		n (%)	N1	18 (9.78)	18 (9.33)
		n (%)	Unknown	7 (3.80)	7 (3.63)
	Clinical staging distant metastasis (M)	n (%)	Blank	38 (20.65)	40 (20.73)
		n (%)	Mx	83 (45.11)	89 (46.11)
		n (%)	M0	43 (23.37)	43 (22.28)
		n (%)	M1	18 (9.78)	18 (9.33)
		n (%)	M1a	0 (0.00)	0 (0.00)
		n (%)	M1b	1 (0.54)	1 (0.52)
		n (%)	M1c	0 (0.00)	1 (0.52)
	Type of treatment	n (%)	Unknown	1 (0.54)	1 (0.52)
		n (%)	Unclassified	38 (20.65)	40 (20.73)
		n (%)	1 - Surveillance (no treatment)	13 (7.07)	14 (7.25)
		n (%)	2 - Androgen Deprivation Therapy (ADT or ADT) [orchiectomy; LHRH agonist or antagonist]	64 (34.78)	65 (33.67)
		n (%)	3 - TPA + 1st generation antiandrogen (> 2 weeks [Bicalutamide; Flutamide or Nilutamide/cyproterone acetate; megestrol acetate; medroxyprogesterone acetate]);	0 (0.00)	0 (0.00)
		n (%)	4 - TPA + chemotherapy	1 (0.54)	1 (0.52)
		n (%)	5 - TPA + new hormonal agents (NHT) [Apalutamide; Darolutamide; Enzalutamide or Abiraterone]	0 (0.00)	0 (0.00)
		n (%)	6 - local treatment [PR; RT]	65 (35.33)	70 (36.27)
	Time interval between BCR and initiation of 1st line of treatment post-BCR	n (%)	7 - Other	2 (1.09)	2 (1.04)
		n (%)	8 - Unclassified	39 (21.20)	41 (21.24)
	Time interval between BCR and initiation of 1st line of treatment post-BCR	Mean ± std		47.72 ± 27.60	51.91 ± 33.10
		Median [IQR]		43.84 [25.43, 63.26]	44.73 [26.15, 69.24]
	Time interval between BCR and initiation of 1st line of treatment post-BCR	Range	months	5.78 – 119.21	5.77 – 169.71

Regarding the BCR calculation, one year was calculated as days/365.25 rounded up to 1 significant digit. The whole sample is 10-year BCR + over 10-year BCR patients.

Table 15: First-Line Treatment post-BCR characteristics in patients progressing to mHSPC (high and low volume) and nmHSPC (high and low risk).

Category	Variables	mHSPC			nmHSPC		
		High volume (N=5)	Low volume (N=30)	Whole sample (N=39)	High risk (N=35)	Low risk (N=50)	Whole sample (N=96)

First-Line Treatment post-BCR Characteristics	Clinical stage before initiation 1st-line treatment post-BCR	I	n (% of population)	n (% of population)	n (% of population)	n (% of population)	n (% of population)	n (% of population)
		II	n (% of population)	n (% of population)	n (% of population)	n (% of population)	n (% of population)	n (% of population)
		III	n (% of population)	n (% of population)	n (% of population)	n (% of population)	n (% of population)	n (% of population)
		IV	n (% of population)	n (% of population)	n (% of population)	n (% of population)	n (% of population)	n (% of population)
		Unknown	n (% of population)	n (% of population)	n (% of population)	n (% of population)	n (% of population)	n (% of population)
	Clinical staging primary tumor (T)	Tx	4 (80.00)	14 (46.67)	18 (46.15)	11 (31.43)	14 (28.00)	29 (30.21)
		T0	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		T1	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		T1a	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		T1b	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.86)	0 (0.00)	1 (1.04)
		T1c	0 (0.00)	0 (0.00)	1 (2.56)	0 (0.00)	0 (0.00)	0 (0.00)
		T2	0 (0.00)	2 (6.67)	2 (5.13)	2 (5.71)	3 (6.00)	5 (5.21)
		T2a	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		T2b	0 (0.00)	0 (0.00)	0 (0.00)	2 (5.71)	3 (6.00)	5 (5.21)
		T2c	0 (0.00)	6 (20.00)	7 (17.95)	3 (8.57)	9 (18.00)	15 (15.63)
		T3	1 (20.00)	3 (10.00)	4 (10.26)	3 (8.57)	1 (2.00)	5 (5.21)
		T3a	0 (0.00)	1 (3.33)	2 (5.13)	3 (8.57)	3 (6.00)	8 (8.33)
		T3b	0 (0.00)	2 (6.67)	2 (5.13)	4 (11.43)	2 (4.00)	6 (6.25)
		T4	0 (0.00)	1 (3.33)	1 (2.56)	0 (0.00)	0 (0.00)	0 (0.00)
		Unclassified	0 (0.00)	1 (3.33)	2 (5.13)	6 (17.14)	15 (30.00)	22 (22.92)
	Clinical staging regional lymph nodes (N)	Nx	3 (60.00)	16 (53.33)	20 (51.13)	11 (31.43)	19 (38.00)	37 (38.54)
		N0	0 (0.00)	3 (10.00)	5 (12.82)	13 (37.14)	14 (28.00)	29 (30.21)
		N1	2 (40.00)	7 (23.33)	9 (23.08)	4 (11.43)	1 (2.00)	5 (5.21)
		Unknown	0 (0.00)	3 (10.00)	3 (7.69)	1 (2.86)	1 (2.00)	3 (3.13)
		Unclassified	0 (0.00)	1 (3.33)	2 (5.13)	6 (17.14)	15 (30.00)	22 (22.92)
	Clinical staging distant metastasis (M)	Mx;	0 (0.00)	9 (30.00)	11 (28.20)	13 (37.14)	24 (48.00)	44 (45.83)
		M0	0 (0.00)	6 (20.00)	7 (17.95)	15 (42.86)	11 (22.00)	29 (30.21)
		M1	5 (100.00)	11 (36.67)	16 (41.02)	1 (2.86)	0 (0.00)	1 (1.04)
		M1a	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		M1b	0 (0.00)	1 (3.33)	1 (2.56)	0 (0.00)	0 (0.00)	0 (0.00)
		M1c	0 (0.00)	1 (3.33)	1 (2.56)	0 (0.00)	0 (0.00)	0 (0.00)
		Unknown	0 (0.00)	1 (3.33)	1 (2.56)	0 (0.00)	0 (0.00)	0 (0.00)
		Unclassified	0 (0.00)	1 (3.33)	2 (5.13)	6 (17.14)	15 (30.00)	22 (22.92)
	Type of treatment	1 - Surveillance (no treatment)	0 (0.00)	0 (0.00)	1 (2.56)	0 (0.00)	4 (8.00)	6 (6.25)
		2 - Androgen Deprivation Therapy (ADT or ADT) [orchiectomy; LHRH agonist or antagonist]	5 (100.00)	21 (69.99)	27 (69.23)	14 (40.00)	12 (24.00)	28 (29.17)
		3 - TPA + 1st generation antiandrogen (> 2 weeks) [Bicalutamide; Flutamide or	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

	Nilutamide/cypro- terone acetate; megestrol acetate; medroxyprogeste- rone acetate]); 4 - TPA + chemotherapy 5 - TPA + new hormonal agents (NHT) [Apalutamide; Darolutamide; Enzalutamide or Abiraterone] 6 - local treatment [PR; RT] 7 - Other 8 - Unclassified	0 (0.00)	1 (3.33)	1 (2.56)	0 (0.00)	0 (0.00)	0 (0.00)
		0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		0 (0.00)	7 (23.33)	8 (20.56)	13 (37.14)	18 (36.00)	37 (38.54)
		0 (0.00)	0 (0.00)	0 (0.00)	2 (5.71)	0 (0.00)	2 (2.08)
		0 (0.00)	1 (3.33)	2 (5.13)	6 (17.14)	16 (32.00)	23 (23.96)
Time interval between BCR and initiation of 1st line of treatment post- BCR	months	41.15 ± 26.37 38.59 [26.78, 43.38] 13.45 – 83.54	46.17 ± 31.18 39.33 [22.60, 51.91] 11.29 – 141.46	45.40 ± 30.12 38.59 [23.54, 51.48] 11.29 – 141.46	37.53 ± 21.48 31.14 [22.36, 49.68] 7.55 – 90.40	53.74 ± 26.89 50.10 [34.79, 65.28] 13.71 – 126.53	48.57 ± 28.89 43.84 [26.16, 61.67] 7.55 – 144.48

Since it is post BCR, the whole means patients with BCR within 5 years + patients with BCR after 5 years.
Regarding the BCR calculation, one year was calculated as days/365.25 rounded up to 1 significant digit. One
month was calculated as days/30.475 rounded up to 1 significant digit.

Table 16: Analysis of time-to-BCR for the nmHSPC patients.

	High risk (N=52)	Low risk (N=71)
Time-to-5 year BCR		
Events, n (%)	52 (100.00)	71 (100.0)
Censored, n (%)	0 (0.00)	0 (0.00)
Median (months) estimated by Kaplan-Meier method	27.73	36.98
95% CI for median (months)	(22.25, 37.54)	(31.50, 42.59)
P-value based on a log-rank test	0.04	
Schoenfeld test (p value)	0.44	
Hazard ratio estimated by Cox PH model	0.69	
95% CI for hazard ratio	(0.48, 0.99)	
	High risk (N=63)	Low risk (N=107)
Time-to-10-year BCR		
Events, n (%)	63 (100.00)	107 (100.0)
Censored, n (%)	0 (0.00)	0 (0.00)
Median (months) estimated by Kaplan-Meier method	32.26	46.92
95% CI for median (months)	(26.32, 43.94)	(42.59, 54.77)
P-value based on a log-rank test	<0.001	
Schoenfeld test (p value)	0.53	
Hazard ratio estimated by Cox PH model	0.56	
95% CI for hazard ratio	(0.41, 0.77)	

No patients were censored in this analysis. Patients with negative PSA values were classified as low risk, as discussed with Astellas' team. High-risk patients were identified as those with PSADT \leq 9 months, while low-risk patients were those with PSADT > 9 months.

Table 17: Analysis of time from BCR to first line treatment by risk status for patients who have had BCR.

	High risk (N=48)	Low risk (N=54)
Events, n (%)	48 (100.00)	55 (100.0)
Censored, n (%)	0 (0.00)	0 (0.00)
Median (months) estimated by Kaplan-Meier method	29.81	40.59
95% CI for median (months)	(22.48, 38.59)	(33.99, 50.27)
P-value based on a log-rank test	0.007	
Schoenfeld test (p value)	0.94	
Hazard ratio estimated by Cox PH model	0.57	
95% CI for hazard ratio	(0.38, 0.86)	

No patients were censored in this analysis. Patients with negative PSA values were classified as low risk, as discussed with Astellas' team. Patients whose reported first-line treatment date precedes the calculated biochemical recurrence (BCR) date were excluded from the model. High-risk patients were identified as those with PSADT \leq 9 months, while low-risk patients were those with PSADT > 9 months.

The variable 'Last PSA previous to post-BCR first-line treatment' and the categorical variables were excluded from the model due to insufficient representation of the response variable by the categories of explanatory variables. This inadequacy is evident, for example, but not limited to, the clinically expected occurrence where the Gleason (2 and 5 for both degrees) and ISUP categories displayed values of 0 in the 'no_treatment' group. As a result, the model's coefficients produced unrealistically high values.

Table 18: Association between type of post BCR treatment and clinical/pathological characteristics.

	Local treatment			Systemic treatment		
	OR	95 % CI	p value	OR	95 % CI	p value
Age at PCa diagnosis	0.81	[0.69, 0.94]	0.005	0.87	[0.76, 1.01]	0.06
Surgical margin status	-	[-, -]	-	-	[-, -]	-
Lymph node invasion	-	[-, -]	-	-	[-, -]	-
Gleason score	-	[-, -]	-	-	[-, -]	-
ISUP grade	-	[-, -]	-	-	[-, -]	-
Pathologic T stage	-	[-, -]	-	-	[-, -]	-
PSA-DT	0.94	[0.91, 0.99]	0.01	0.96	[0.93, 0.99]	0.01
Pre-definitive treatment PSA	0.94	[0.91, 0.98]	0.005	0.99	[0.96, 1.01]	0.24
Interval to biochemical failure	0.48	[0.30, 0.75]	0.002	0.51	[0.33, 0.78]	0.002
Last PSA previous to post-BCR first-line treatment	-	[-, -]	-	-	[-, -]	-
Last clinical staging previous to post-BCR first-line treatment	-	[-, -]	-	-	[-, -]	-

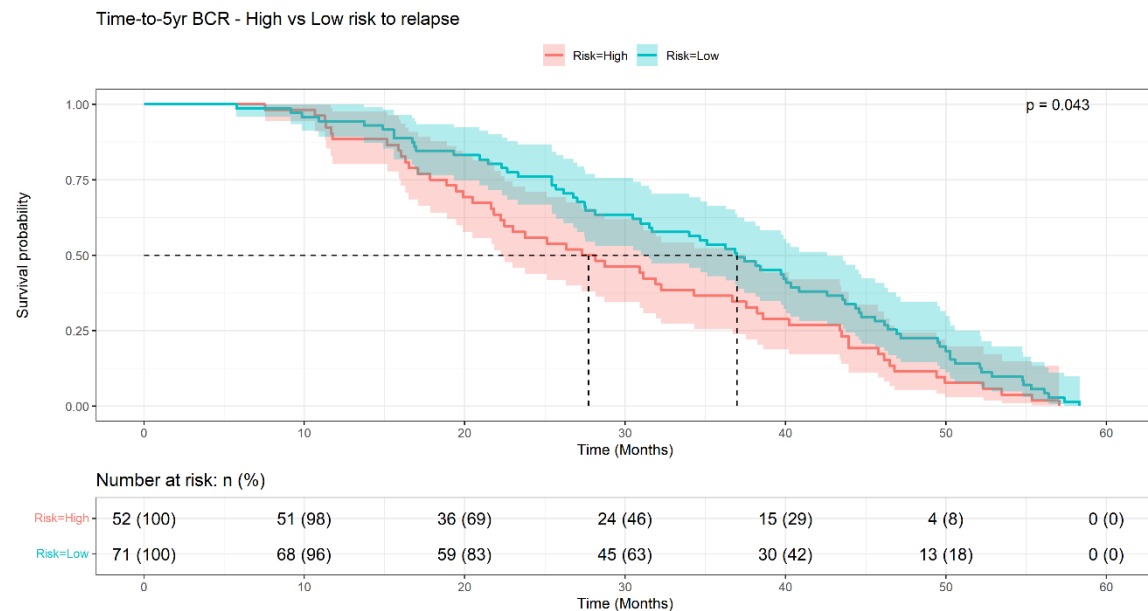
Analysis is performed using a multinomial logistic regression with type of treatment (local, systemic, no treatment) as a response variable, clinical/pathological characteristics as fixed effects of covariates. The reference group for response variable is "no treatment", resulting in two models to be tested: 1) one comparing the local versus no treatment, $\ln\{\text{Pr}(\text{local treatment})/\text{Pr}(\text{no treatment})\}$, and 2) the other one comparing the systemic versus no treatment, $\ln\{\text{Pr}(\text{systemic treatment})/\text{Pr}(\text{no treatment})\}$. This is the final model ($p < 0.001$) after a forward stepwise. The '-' signifies the variable that did not enter the model due to insufficient representativeness. The description of these variables is presented in the annex 3.

10.4 Main Results

In accordance with the SAP, below are presented all figures, including those pertaining to High vs Low volume, despite limited data availability for the high-volume group.

Figure 4: Kaplan-Meier plot of the time-to-BCR for low-risk (PSADT > 9 months) vs high-risk (PSADT ≤ 9 months) patients (nmHSPC). a) time-to-5yr BCR; b) time-to-10yr BCR.

A)



B)

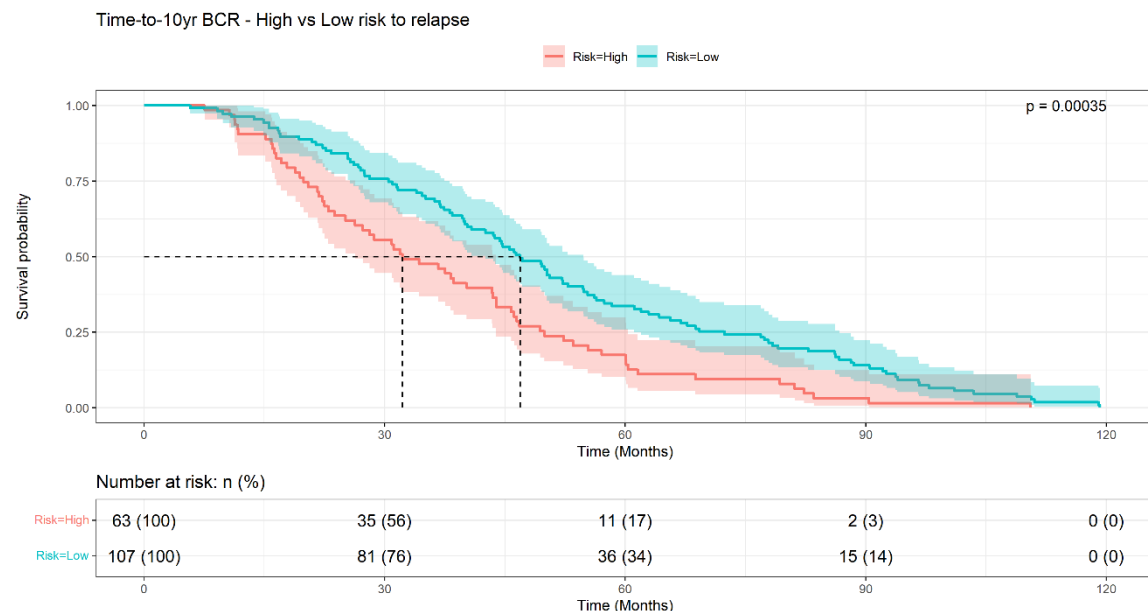
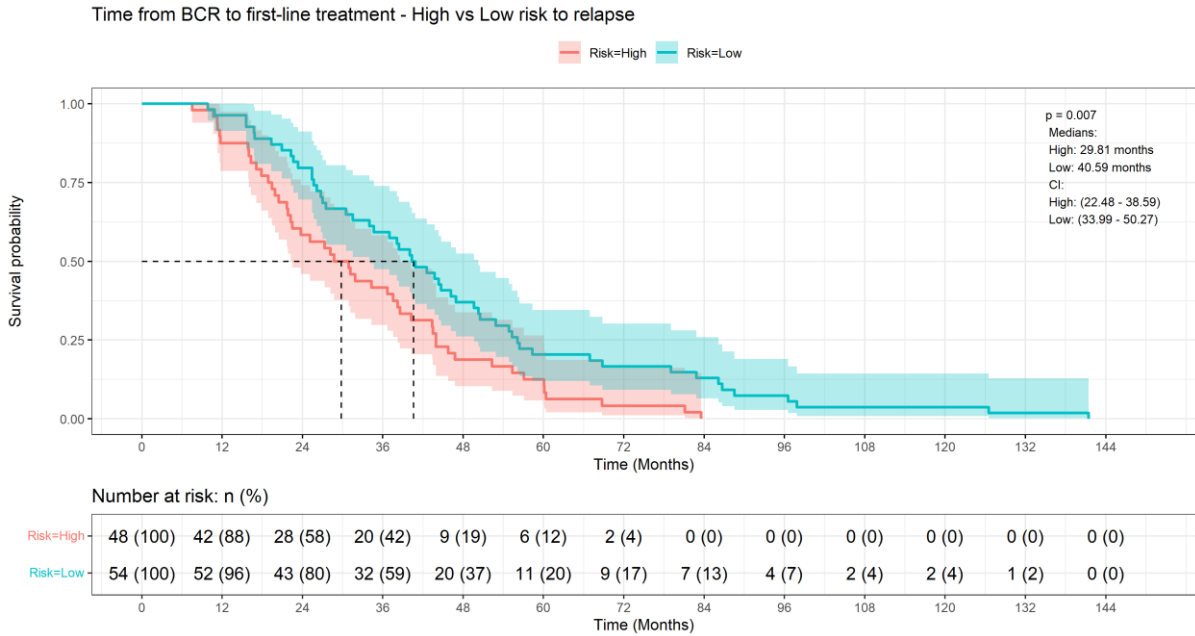


Figure 5: Kaplan-Meier plot of the time from BCR to initiation of first-line treatment for low- vs high-risk patients (nmHSPC).



10.5 Other Analyses

None.

10.6 Adverse Events/Adverse Reactions

There were no adverse events reports for this study.

11 DISCUSSION

11.1 Key Results

11.2 Limitations

The limitations of this study are associated with the nature of the real-world data. While Electronic Medical Record (EMR) data are valuable for the efficient and effective examination of patient profiles and treatment patterns, only patients from the single site (Hospital Erasto Gaertner) were included in the study, and results may not be generalizable to the PCa population in Brazil.

EMR do not provide homogeneous data collection and some missing data were expected. However, the proposed variables for this study were data usually recorded in medical charts and laboratory and imaging reports, so we did not foresee unusual limitations in data collection. Death was not expected in this stage due to PCa, so we did not expect a considerable number of deaths. The number of death events was assessed, analyzed, and reported. Patients moving out (referrals to other institutions) were also not expected, due to the nature of the public health system in Brazil. The proportion of patients without required follow-up was checked, analyzed, and reported as well.

11.3 Interpretation

11.4 Generalizability

The inclusion of patients from a single site in the southern region of Brazil affects the representativeness and external validity for the entire country. Indeed, the findings regarding the ethnicity of the sample may not accurately represent the Brazilian setting.

12 OTHER INFORMATION

Not applicable.

13 CONCLUSIONS

14 REFERENCES

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15 ANNEXES

Annex 1 List of stand-alone documents

Document	Version	Date	Comments
Protocol	v2.0	10 May 2023	Document in its last version.
Statistical Analysis Plan (SAP)	v3.0	10 May 2023	Document in its last version.
Electronic Case Report File (eCRF)	v5.0	09 Nov 2022	Document in its last version.

Annex 2 List of IECs/IRBs with dates of approval

Site # / Investigator	IEC/IRB Name and Address	Date(s) of approval
Site #001, Murilo de Almeida Luz, MD	Hospital Erasto Gaertner Independent Ethics Committee 201 Dr. Ovande do Amaral St, Curitiba/PR, 81520-060	13 Feb 2023

Annex 3 Description of the variables excluded from the Multinomial model due to insufficient representativeness.

Surgical margin

	blank	Unknown	Negative	Positive
No_treatment	12	0	1	1
Local_treatment	5	1	21	43
Systemic_treatment	46	1	14	7

Stage T

	blank	T2	T3
No_treatment	14	0	0
Local_treatment	66	4	0
Systemic_treatment	60	3	5

Gleason 1

grupo	2	3	4	5
No_treatment	0	9	5	0
Local_treatment	1	47	20	2
Systemic_treatment	0	32	33	3

Gleason 2

	2	3	4	5
No_treatment	0	6	8	0
Local_treatment	1	42	26	1
Systemic_treatment	0	24	37	7

ISUP

	1 (Gleason 2-6)	2 (Gleason 7 (3+4))	3 (Gleason 7 (4+3))	4 (Gleason 8)	5 (Gleason 9-10)
No_treatment	4	5	2	3	0
Local_treatment	33	15	10	9	3
Systemic_treatment	12	20	12	15	9

Lymphonode invasion

	blank	Unknown	No	Yes
No_treatment	12	0	2	0
Local_treatment	5	19	46	0
Systemic_treatment	46	8	8	6

T – It would not be feasible, even with grouping (T1, T2, T3, T4)

grupo	blank	T1b	T2	T2b	T2c	T3	T3a	T3b	T4	Tx
No_treatment	14	0	0	0	0	0	0	0	0	0
Local_treatment	23	1	5	3	15	3	8	2	0	10
Systemic_treatment	6	0	3	0	5	4	1	4	2	43

N

	blank	Unknown	N0	N1	Nx
No_treatment	14	0	0	0	0
Local_treatment	23	2	24	2	19
Systemic_treatment	6	2	7	14	39

M

	blank	Unknown	M0	M1	M1b	M1c	Mx
No_treatment	14		0	0	0	0	0
Local_treatment	23		0	16	1	0	29
Systemic_treatment	6		1	19	14	1	27

Signatures

COORDINATING INVESTIGATOR'S SIGNATURE

I have read all pages of this final clinical study report for which Astellas is the Sponsor. I have read this study report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study.

Coordinating Investigator:

Signature:

Name (Printed):

Date (dd-Mmm-YYYY)

Department/
Affiliation:

Address of
Institution:

KEY CONTRIBUTORS

The following contributors reviewed this final Study Report with respect to consistency, completeness and traceability of the scientific content, as well as for the accurate representation of the data/information and its interpretation in the document, as relevant to their indicated discipline or role.

Name, Degree and Title	Department
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Name, Degree and Title	Department
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Name, Degree and Title	Department
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ASTELLAS SIGNATORIES

(electronic signatures are attached at the end of the document)

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study.

Name, Degree, and Title

<Medical Lead or HEOR Lead (for HEOR-led studies)>

Signature

Date (dd-Mmm-yyyy):

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study.

Name, Degree, and Title

<Study Manager>

Signature

Date (dd-Mmm-yyyy):

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study.

Name, Degree, and Title

<Study Statistician>

Signature

Date (dd-Mmm-yyyy):

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study.

Name, Degree, and Title

<Regional CMT Member or CMT Lead >

Signature

Date (dd-Mmm-yyyy):

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study.

Name, Degree, and Title

<PV-PRP >

Signature

Date (dd-Mmm-yyyy):

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study.

Name, Degree, and Title

<EU-QPPV >

Signature

Date (dd-Mmm-yyyy):

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study.

Name, Degree, and Title

<TAH / VP Medical Sciences / Head CPED >

Signature

Date (dd-Mmm-yyyy):