AstraZeneca

CLINICAL STUDY REPORT

DRUG SUBSTANCE	NA
STUDY CODE	NIS-OGR-DUM-2007/1
VERSION NUMBER	1.0
DATE	23 FEBRUARY 2010

Study Title: A retrospective epidemiological study aiming to describe the socio-demographic and clinical characteristics of patients diagnosed with locally advanced or metastatic prostate cancer, as well as the therapeutic algorithm followed in Greek clinical practice

STUDY DATES	Date of 1st Patient enrolled: January 5th, 2008 Date of Last Patient Completed: March 25th, 2009
PHASE OF DEVELOPMENT	Epidemiological, Retrospective Study

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and specific terms are used in the present clinical study report

Abbreviation	**Explanation**
CAB	Complete Androgen Blockade
CNB	Core Needle Biopsy
CRF	Case Report Form
3D-CRT	3D-Conformal Radiotherapy
CT	Computer Tomography
DRE	Digital Rectal Examination
EBRT	External Beam Radiation
EOF	National Organization for Medicines (in Greece)
FNA	Fine needle aspiration
GCP	Good Clinical Practice
HDR brachytherapy	High Dose Rate Brachytherapy
HIFU	High Intensity Focused Ultrasound
ICH	International Conference on Harmonisation
IMRT	Intensity-Modulated Radiation Therapy
IRB	Institutional Review Board (Hospital Scientific Committee/Administrative Council)
LDR brachytherapy	Low Dose Rate Brachytherapy
LH-RHA	Luteinising Hormone Releasing Hormone analogues
PAB	Peripheral Androgen Blockade
MRI	Magnetic Resonance Imaging
PSA	Prostate Specific Antigen
RITA	Radiofrequency Interstitial Tumour Ablation
SD	Standard Deviation
SPC	Summary of Product Characteristics
TRUS	Transrectal Ultrasonography

2 ETHICS

2.1 Review and approval by the competent authorities

The final study protocol, including the final version of the Patient's Informed Consent Form, have been approved by the competent IRB (Scientific Committee/Administrative Council) of the participating Hospital Sites and the National Organization for Medicines (EOF), before the enrolment of any patient into the study and the performance of any study related procedure. All study amendments and/or administrative changes pertaining to the approved protocol have been also submitted to EOF for approval.

2.2 Ethical conduct of the study

The study has been conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (ICH-GCP guidelines), all applicable national and E.U. laws and regulations, and AstraZeneca policy on Bioethics.

2.3 Subject information and consent

This study aimed exclusively at the retrospective collection of information from patient medical records, which was obtained during the routine clinical management of patients. In accordance with national provisions before conducting any study-related activity, the investigator should provide the patient (or his legal representative, if required) oral and written information regarding the study. Therefore, prior to the collection and record of any study related data, investigators ensured that each potential participating patient had been provided with accurate and adequate oral and written information about the nature, purpose, possible risks and benefits of the present study. Additionally, patients were informed regarding their right to discontinue their participation in the study at any time and for any reason. They have been given the opportunity to ask questions on the nature and purpose of the study and all study-related procedures, as well as adequate time for consideration whether or not they wish to participate in the study. The patient's signed informed consent form (ICF), if available, was obtained in duplicate before enrolling the patient into the study. The original signed ICF was archived by the investigator while a copy of the signed ICF was provided to the patient.

3 INTRODUCTION

Prostate cancer is a multifocal disease with long-term natural history presenting with various clinical manifestations and forms ranging from clinically localized to metastatic and from hidden or latent form to clinically evident cancer with significant impact on quality of life of patients. It is a major public health problem since it affects approximately 70 to 80% of men aged 80 years and older, and is the most common malignancy among men over 50 years of the Western world (particularly in the U.S. and Europe) and second leading cause of cancer death, leading to one death every 17 minutes [1,2].

Early detection and timely prognosis of the evolutionary progress of prostate cancer are the main goals of longitudinal clinical and laboratory research. In addition, the better understanding of the demographic, clinical, morphological and genetic characteristics of patients aims at improving the therapeutic strategies for the management of the disease. Despite the substantial social burden and economic consequences of prostate cancer in Greece the literature data on the epidemiological and clinical characteristics and therapeutic algorithm used for the treatment of patients with prostate cancer are limited.

In this setting, the present epidemiological study was designed aiming at depicting the current epidemiological, clinical, diagnostic and therapeutic features of the disease, in order to assess the impact of various factors in the optimal control of prostate cancer.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Study primary objective and primary endpoints

The primary objective of this epidemiological study was to record the socio-demographic and clinical characteristics of patients diagnosed with locally advanced or metastatic prostate cancer and to describe the therapeutic algorithm followed in Greece in everyday clinical practice.

4.2 Study secondary objectives and secondary endpoints

The secondary objectives of the study referred to the evaluation of the impact of established prognostic factors in treatment decisions as well as the assessment of associated risk factors in disease progression.

5 INVESTIGATIONAL PLAN AND PROCEDURES

5.1 Overall study design

This is a local multicentre, epidemiological, retrospective study of patients diagnosed with locally advanced or metastatic prostate cancer in Greece. This study has been conducted by 28 hospital and office-based physicians. The data have been collected by 310 subjects who met the study eligibility criteria. All required information for each patient has been documented in one visit.

All information regarding eligible patients has been recorded by the physicians in case report forms (CRFs).

For the evaluation of study objectives the following data have been collected and recorded:

- Somatometric data (age, weight, height);
- Sociodemographics (race, level of education, occupational status, living conditions, place of residence at the time of diagnosis);
- Dietary habits / smoking history and alcohol consumption/ sexual activity / physical activity;
- Medical history, co-morbidities, and family history;
- Prostate cancer history including the following:
    - Diagnostic methodology used (DRE, PSA, Transrectal Ultrasound, MRI, CT scan, bone scan, histological examination);
    - Levels of total and free PSA as well as PSA density at diagnosis;
    - Total and free testosterone at diagnosis;
    - Date of initial diagnosis of prostate cancer and date of diagnosis of locally advanced or metastatic prostate cancer;
    - Types of biopsy procedures followed at diagnosis [FNA, CNB, transrectal, transurethral, transperineal, surgical biopsy], and number of biopsies performed;
    - Primary tumor location and size;
    - Histological grading of prostate adenocarcinoma (Gleason score);
    - Staging of prostate cancer using TNM classification;
    - Histopathological grading (G);
    - Filtration of adjacent pelvic lymph nodes and sites of metastasis;
- Therapeutic management of prostate cancer including details on:
    - Surgical therapy
    - Radiation therapy
    - Topical therapy

- Watchful waiting
- Hormone therapy
- Chemotherapy
- Biological therapy/immunotherapy

5.2 Discussion of study design and non-interventional type of the study

This was a local, multicentre, epidemiological, retrospective, single-visit study of patients with locally advanced or metastatic prostate cancer across Greece.

5.3 Selection of study population

5.3.1 Inclusion criteria

- Patients with confirmed locally advanced (T3-T4 N0, M0, T1-4 N1 M0) or metastatic (any T, any N, M1) prostate cancer;
- Patients who were initially diagnosed with prostate cancer after 2002;
- Patients receiving or have received hormonal therapy for prostate cancer.

5.3.2 Exclusion criteria

- Men under 18 years old

5.3.3 Subjects' withdrawal of treatment or assessment

NA

6 STATISTICAL ANALYSIS PLAN AND SAMPLE SIZE DETERMINATION

As this is an epidemiological study, statistical analysis of collected data, including baseline sociodemographic and somatometric data, as well as study endpoints and outcome variables, was performed using appropriate descriptive statistical methods.

6.1 Determination of sample size

The sample size of approximately 310 evaluable patients was considered sufficient to meet the primary objective of this protocol with a high statistical power.

6.2 Statistical and analytical methods

Summary statistics were used to present the data of this study. Specifically, the mean value, the standard deviation, the median value and the range (minimum - maximum values) were used for the analysis and the presentation of continuous variables. Categorical variables were summarized as frequency distribution tables and relevant percentages.
Data processing and analysis were performed using the statistical package SPSS v. 17.0.

6.3 Description of analysis sets

Statistical Analysis was performed for the total of 310 subjects who participated in the study, as anticipated by the clinical study protocol.

6.4 Statistical and analytical considerations

For the analysis of study measures the 'Full Analysis Set' has been used, which is defined as all patients who were enrolled in the study. Missing data were not imputed.

7 STUDY SUBJECTS

7.1 Subjects who participated and completed the study

Overall 310 subjects participated and completed the present study, and were enrolled by 28 investigational sites (6 hospital and 22 office-based urologists).

7.2 Protocol deviations

No protocol deviations were observed in the current study.

7.3 Subjects analyzed

Overall 310 subjects were analyzed.

8 RESULTS

8.1 Analysis of subjects somatometric and sociodemographic characteristics

8.1.1 Subjects' somatometric characteristics

Table 1 presents the summary statistics of subjects' somatometric data. Subjects that participated in the study had a mean age of 72.0±8.8 years, where the youngest and the oldest patients were

37.0 and 94.0 years old, respectively. No extreme values regarding their height and weigh were reported.

Table 1 Descriptive Statistics of Somatometric Data

Somatometric Data	Mean	Std Dev	Median	Minimum	Maximum	N
Age (years)	72.0	8.8	72.0	37.0	94.0	308
Weight (kg)	80.0	9.4	80.0	54.0	110.0	295
Height (cm)	171.9	9.0	172.0	75.0	190.0	295

8.1.2 Subjects' socio-demographic data

Almost all the participants in the study were white, with the exception of one patient who was Asian. [Table 2]

Table 2 Distribution of Patients by Race

Race	n	%
White	306	98.7%
Asian	1	0.3%
Black	0	0.0%
Other	0	0.0%
Missing	3	1.0%
Total	310	100.0%

More than half of the study participants (57.4%) had primary to lower secondary education whereas 39.7% had at least upper secondary education. [Table 3]

Table 3 Distribution of Patients by Level of Education

Level of Education	n	%
Primary	103	33.2%
Lower secondary (gymansium)	75	24.2%
Upper secondary (lyceum)	58	18.7%
Higher education	31	10.0%
Highest education (tertiary)	34	11.0%
Missing	9	2.9%
Total	310	100.0%

More than half of the study participants (66.1%) were residents of urban areas. [Table 4]

Table 4 Distribution of Patients According to their Place of Residence

Place of Residence During Prostate Cancer Diagnosis	n	%
Urban area	205	66.1%
Rural area	99	31.9%
Missing	6	1.9%
Total	310	100.0%

74.5% of the patients were living in Greece when the prostate cancer was diagnosed, and only 2 of them were residents of different countries (Germany and USA, respectively). [Table 5]
The mean duration of residence in the above countries was 34.6 ±23.6 years [Median: 20.0 years, min-max: 10.0-67.0 years].

Table 5 Distribution of Patients According to their Country of Residence

Country of Residence During Prostate Cancer Diagnosis	n	%
Greece	231	74.5%
Other	2	0.6%
Missing	77	24.8%
Total	310	100.0%

The vast majority of the patients were married (80.0%) and the second higher percent in the marital status distribution was the widower ones (11.6%), which was expected, considering the mean age of our sample. [Table 6]

Table 6 Distribution of Patients According to their Marital Status

Marital Status	n	%
Unmarried	11	3.5%
Married	248	80.0%
Divorced	11	3.5%
Widower	36	11.6%
Missing	4	1.3%
Total	310	100.0%

181 out of 310 patients were retired (58.4%) and only 27.4% were employed. Also, there were 3 monks among the study participants. [Table 7]

Table 7 Distribution of Patients According to their Employment Status

Employment Status	n	%
Unemployed	34	11.0%
Employed	85	27.4%
Other	184	59.4%
Missing	7	2.3%
Total	310	100.0%

8.1.3 Subjects lifestyle patterns

8.1.3.1 Consumption of fat, vegetables, soya and green tea

Regarding their dietary habits, 79.3% of the patients reported moderate to high dietary fat intake while 80.4% of them reported moderate to high consumption of vegetables, soya and green tea. [Table 8]

Table 8 Distribution of Patients According to the Consumption of Fat, Vegetables, Soya and Green Tea

Dietary habits	High Intake		Moderate Intake		Not at All		Missing		Total	
	n	%	n	%	n	%	n	%	n	%
Consumption of fat	67	21.6%	179	57.7%	33	10.6%	31	10.0%	310	100.0%
Consumption of Vegetables, Soya and Green Tea	82	26.5%	167	53.9%	30	9.7%	31	10.0%	310	100.0%

8.1.3.2 Smoking habits

More than half of the patients (56.5%) were either current or ex-smokers [Table 9]. The median smoking duration was 30.0 years for both smokers and ex-smokers, and the average number of cigarettes smoked per day was 22.1 (±9.2) and 25.4 (±15.1) for current and ex smokers, respectively. [Table 10]

Table 9 Distribution of Patients According to the Smoking Status

Smoking Habits	n	%
Smoker	97	31.3%
Non smoker	127	41.0%
Ex smoker	78	25.2%
Missing	8	2.6%
Total	310	100.0%

Table 10 Summary Statistics for Smoking

Smoking Habits		Mean	Std Dev	Median	Minimum	Maximum	N
Smokers	Smoking duation (in years)	32.1	11.9	30.0	10.0	60.0	77
	Number of cigarettes/day	22.1	9.2	20.0	2.0	60.0	77
Ex smokers	Smoking duation (in years)	29.4	12.3	30.0	10.0	60.0	61
	Number of cigarettes/day	25.4	15.1	20.0	1.0	100.0	61

8.1.3.3 Alcohol consumption

More than half of the patients (53.9%) were not consuming alcohol [Table 11], and the mean number of glasses of alcoholic beverages consumed per day was 2.0±1.1 [Table 12].

Table 11 Distribution of Patients According to Alcohol Consumption

Alcohol Consumption	n	%
Yes	132	42.6%
No	167	53.9%
Missing	11	3.5%
Total	310	100.0%

Table 12 Summary Statistics for Alcohol Consumption

Alcohol Habits	Mean	Std Dev	Median	Minimum	Maximum	N
Glasses of alcoholic beverages consumed per day	2.0	1.1	2.0	0.5	6.0	121

8.1.3.4 Sexual activity

The mean age at first sexual intercourse was 19.7±3.0 years [Table 13]. 67.4% of the participants had frequent change of sexual partners, while only 7.4% had a sexually transmitted disease. [Tables 14 & 15]

Table 13 Summary Statistics for Sexual Activity

Sexual Activity	Mean	Std Dev	Median	Minimum	Maximum	N
Age at first sexual intercourse (in years)	19.7	3.0	19.0	14.0	30.0	266

Table 14 Distribution of Patients According to their Sexual Activity

Sexual Activity	Yes		No		Missing		Total	
	n	%	n	%	n	%	n	%
Frequent change of sexual partners	209	67.4%	68	21.9%	33	10.6%	310	100.0%
Sexually transmitted diseases	23	7.4%	253	81.6%	34	11.0%	310	100.0%

Table 15 Type & Frequency of Sexually Transmitted Diseases

Type of Sexually Transmitted Diseases (n=23)	n	%
Blennorrhea	9	2.9%
Gonococcal urethritis	4	1.3%
Chronic prostatitis	3	1.0%
Gonorrhoea	3	1.0%
Condylomas	1	0.3%
Leucorrhea-urethritis	1	0.3%
Ureaplasma, chlamydia	1	0.3%
Urethritis	1	0.3%
Total	23	7.4%

8.1.3.5 Physical activity

More than half of the study participants (67.1%) reported moderate to high levels of physical activity. [Table 16]

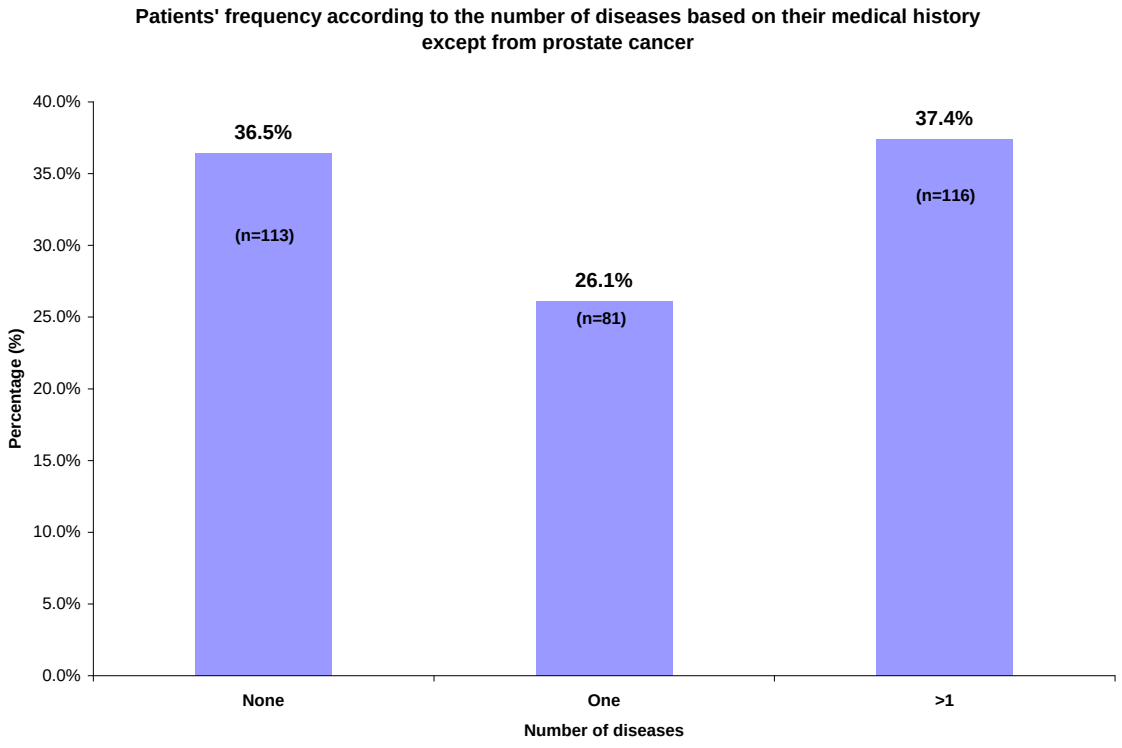
Table 16 Distribution of Patients According to their Physical Activity

Physical Activity	n	%
High	59	19.0%
Moderate	149	48.1%
Not at All	85	27.4%
Missing	17	5.5%
Total	310	100.0%

8.2 Medical history and concomitant diseases

36.5% of the patients didn't suffer from any other disorder except of prostate cancer, while 197/310 (63.5%) reported at least one concomitant disease according to their medical history [Figure 1].

Figure 1 Distribution of Patients with Medical History



Tables 17 and 18 present in detail all concomitant diseases of study participants, based on their medical history and categorized by organ system. Most common concomitant disorders were cardiovascular, cerebrovascular and peripheral vascular diseases reported by 41.6% of study participants.

Table 17 Patients' Medical History by Organ System

Medical History (present or past) Besides Prostate Cancer	n	%
Cardiovascular, Cerebrovascular & Peripheral Vascular Disease	129	41.6%
Gastrointestinal Disease	60	19.4%
Musculoskeletal Disease	48	15.5%
Endocrine-Metabolic Disease	47	15.2%
Respiratory Disease	42	13.5%
Liver-kidney-pancreas disease	19	6.1%
Psychiatric-Neurological Disease	14	4.5%
Neoplasmatic Disease	12	3.9%
Blood and Immune System Disease	10	3.2%
Skin Disease	6	1.9%

Table 18 Description of Concomitant Diseases by Organ System

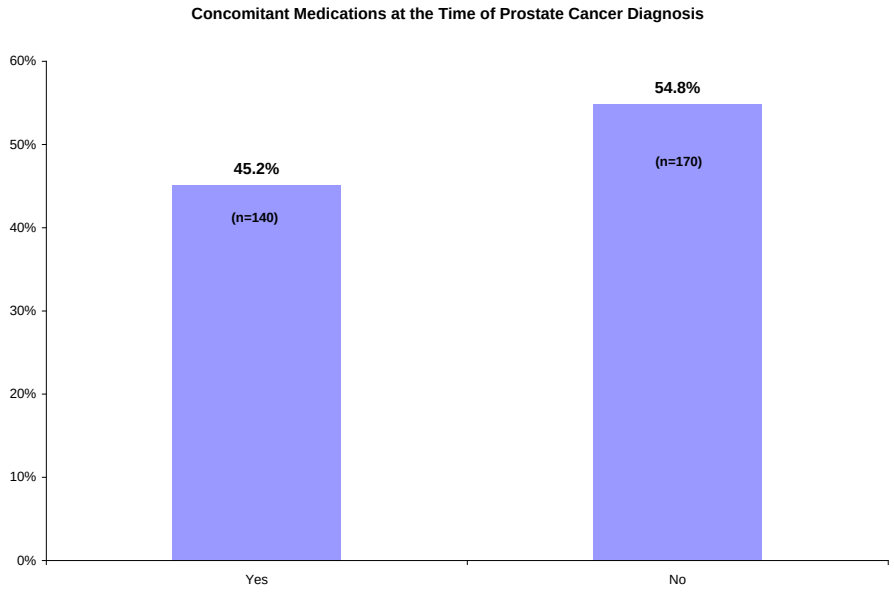
Concomitant Diseases	n	%
Cardiovascular, Cerebrovascular & Peripheral Vascular Disease	**129**	**41.6%**
Arterial hypertension	62	20.0%
Coronary artery disease	39	12.6%
Cardiac arrhythmia	13	4.2%
Myocardial infarction	11	3.5%
Valvular heart disease	4	1.3%
Cerebrovascular accident	3	1.0%
Peripheral vascular disease	3	1.0%
Chronic pulmonary heart disease	1	0.3%
Heart failure	1	0.3%
Missing	14	4.5%
Gastrointestinal Disease	**60**	**19.4%**
Peptic ulcer	21	6.8%
Gastritis	10	3.2%
Ulcerative colitis	6	1.9%
Cholecystectomy	4	1.3%
Gastroesophageal reflux disease	3	1.0%
Irritable bowel syndrome	2	0.6%
Cholelithiasis	1	0.3%
Colorectal polyps	1	0.3%
Diaphragmatic hernia	1	0.3%
Gastrectomy	1	0.3%
Esophagitis	1	0.3%
Gastrorrhagia	1	0.3%
Total removal of small intestine	1	0.3%
Missing	11	3.5%
Musculoskeletal Disease	**48**	**15.5%**
Osteoarthritis	6	1.9%
Arthralgias	4	1.3%
Sciatica	3	1.0%
Spondyloarthritis	3	1.0%
Degenerative spondylopathy	2	0.6%
Rheumatoid arthritis	2	0.6%
Arthritis	1	0.3%
Cervical syndrome	1	0.3%
Discopathy	1	0.3%
Lumbago	1	0.3%
Lumbar spine injury	1	0.3%
Upper limb fractures	1	0.3%
Myosclerosis	1	0.3%
Missing	22	7.1%

Concomitant Diseases (continued 1)	n	%
Endocrine-Metabolic Disease	**47**	**15.2%**
Diabetes mellitus	28	9.0%
Dyslipidemia	8	2.6%
Hyperthyroidism	4	1.3%
Hyperuricemia	3	1.0%
Multinodular goiter	1	0.3%
Missing	8	2.6%
Respiratory Disease	**42**	**13.5%**
COPD	22	7.1%
Bronchial asthma	4	1.3%
Chronic bronchitis	4	1.3%
Chronic respiratory failure	2	0.6%
Pneumonia	2	0.6%
Respiratory allergy	1	0.3%
Tuberculosis	1	0.3%
Missing	7	2.3%
Liver-Kidney-Pancreas Disease	**19**	**6.1%**
Chronic renal failure	5	1.6%
Nephrolithiasis	4	1.3%
Hepatitis	2	0.6%
Echinococcus	1	0.3%
Fatty infiltration of liver	1	0.3%
Hepatic failure	1	0.3%
Kidney donation	1	0.3%
Pyelonephritis	1	0.3%
Missing	3	1.0%
Psychiatric-Neurological Disease	**14**	**4.5%**
Depression	4	1.3%
Psychotic syndrome	4	1.3%
Parkinson's disease	2	0.6%
Anxiety disorder	1	0.3%
Dementia	1	0.3%
Myasthenia	1	0.3%
Missing	1	0.3%

Concomitant Diseases (continued 2)	n	%
Neoplasmatic Disease	**12**	**3.9%**
Bladder cancer	3	1.0%
Colorectal cancer	2	0.6%
Kidney cancer	2	0.6%
Basal cell cancer of nose	1	0.3%
Basal cell skin cancer	1	0.3%
Cervical melanoma	1	0.3%
Lung cancer	1	0.3%
Missing	1	0.3%
Blood and Immune System Disease	**10**	**3.2%**
Anaemia	5	1.6%
Chronic lymphocytic leukemia	1	0.3%
Sickle cell trait	1	0.3%
Missing	3	1.0%
Skin Disease	**6**	**1.9%**
Psoriasis	3	1.0%
Dermatitis	1	0.3%
Vitiligo	1	0.3%
Missing	1	0.3%

45.2% of the study participants were receiving medications for concomitant diseases at the time of prostate cancer diagnosis. [Table 19]

Table 19 Concomitant Medications at the Time of Prostate Cancer Diagnosis



8.3 Family medical history

8.3.1 Family history of prostate cancer

Only 7.1% (22) of the patients had positive family history regarding prostate cancer. [Table 20]

Table 20 Family History of Prostate Cancer

Family Member	Prostate Cancer			
	Negative Family History (n=288)		Positive Family History (n=22)	
	n	%	n	%
	288	92.9%	22	7.1%
Brother	-	-	11	3.5%
Father	-	-	10	3.2%
Grandfather	-	-	1	0.3%

8.3.2 Family history of other neoplasmatic diseases

8.7% (27) of the patients had positive family history of other neoplasmatic diseases [Breast cancer (6), bladder cancer (2), colorectal cancer (5), endometrial cancer (1), laryngeal cancer (1), generalized cancer (1), stomach cancer (3), leukaemia (1), lung cancer (4), pancreatic cancer (1), uterine cancer (2)]. [Table 21]

Table 21 Family History of Other Neoplasmatic Diseases

Family Member	Other Neoplasmatic Diseases			
	Negative Family History (n=283)		Positive Family History (n=27)	
	n	%	n	%
	283	91.3%	27	8.7%
Brother	-	-	8	2.6%
Father	-	-	7	2.3%
Mother	-	-	7	2.3%
Sister	-	-	3	1.0%
Missing	-	-	2	0.6%

8.4 Diagnosis of prostate cancer

8.4.1 Patients' age at initial diagnosis of prostate cancer and at diagnosis of locally advanced or metastatic prostate cancer

Patients' mean age at initial diagnosis of prostate cancer was 69.2 (±8.7) years, and mean age at diagnosis of locally advanced or metastatic cancer was 69.2 (±8.8) years, respectively. Descriptive statistics for patients' age at diagnosis of prostate cancer is presented in Table 22.

Table 22 Summary Statistics for Patients' Age at Initial Diagnosis of Prostate Cancer and at Diagnosis of Locally Advanced or Metastatic Prostate Cancer

Patient's Age	Mean	Std Dev	Median	Minimum	Maximum	N
Patients' age at initial diagnosis of prostate cancer (in years)	69.2	8.7	69.0	37.0	90.0	292
Patients' age at diagnosis of locally advanced or metastatic prostate cancer (in years)	69.2	8.8	69.0	37.0	90.0	222

8.4.2 Time from initial diagnosis to progression to metastatic or locally advanced prostate cancer

Mean time from initial diagnosis to progression to locally advanced or metastatic prostate cancer was 3.47 (±7.66) months, whereas 15.8% (49) of patients were initially diagnosed with locally advanced or metastatic prostate cancer. [Table 23]

Table 23 Mean Time from Initial Diagnosis to Progression to Metastatic or Locally Advanced Prostate Cancer

Variable	Mean	Std Dev	Median	Minimum	Maximum	N
Time from initial diagnosis to progression to locally advanced or metastatic cancer (in months)	3.47	7.66	0.51	0.00	51.68	202

8.4.3 Diagnostic methods used for the detection of prostate cancer

PSA screening was the most commonly used method (97.4%) for the detection of prostate cancer. In 81 % (251) of study participants PSA screening, digital rectal examination (DRE), and histological examination were used for prostate cancer diagnosis, while 63.8% (198) of patients underwent PSA testing, DRE, transrectal ultrasound (TRAS), histological examination, CT scan and bone scan. [Table 24]

Table 24 Distribution of Patients According to Diagnostic Methodology Used

Diagnostic Methods	n	%
PSA	302	97.4%
DRE	279	90.0%
Histological Examination	275	88.7%
Bone Scan	268	86.5%
CT	254	81.9%
Transrectal Ultrasound	252	81.3%
MRI	27	8.7%

8.4.4 Total PSA, Free PSA, Free/total PSA ratio (%), PSA Density, Total Testosterone & Free Testosterone level at diagnosis

Median total PSA level of study participants at diagnosis was 14.6 ng/mL, median free to total PSA ratio was 0.15, median PSAD was 0.45 ng/ml/cm^3, and median total testosterone level was 4.79 ng/mL.

Table 25 Descriptive Statistics of total PSA, Free PSA, Free/total PSA ratio (%), PSA Density, Total Testosterone and Free Testosterone level at diagnosis

Variables (at diagnosis)	Mean	Std Dev	Median	Minimum	Maximum	N
Total PSA (ng/mL)	43.74	126.74	14.60	0.26	1214.00	308
Free PSA (ng/mL)	13.30	64.92	1.50	0.01	530.00	114
Free/total PSA ratio (%)	0.19	0.15	0.15	0.00	0.62	114
PSA Density (ng/ml/cm^3)	1.04	1.08	0.45	0.17	4.00	20
Total Testosterone (ng/mL)	13.57	63.00	4.79	1.85	450.00	50
Free Testosterone level (ng/mL)	1.06	3.17	0.07	0.01	10.10	10

8.4.5 Type of biopsy procedure and number of biopsies performed

Table 26 presents the distribution of patients according to the type of biopsy procedure. Transrectal was the most frequent prostate biopsy procedure performed (87.4%).

Table 26 Distribution of Patients According to the Type of Biopsy Procedures

Type of Biopsy Procedure	n	%
Fine-needle aspiration (FNA)	33	10.6%
Core-Needle biopsy (CNB)	42	13.5%
Surgical	8	2.6%
Transrectal	271	87.4%
Transurethral	9	2.9%
Transperineal	4	1.3%

The mean number of biopsies that study participants underwent was 10.0 (±6.7). [Table 27]

Table 27 Descriptive Statistics for the Number of Biopsies Performed

Variable	Mean	Std Dev	Median	Minimum	Maximum	N
Number of Biopsies	10.0	6.7	11.0	1.0	30.0	197

8.4.6 Location of the primary prostate tumor

Table 28 presents the distribution of the location of the primary prostate tumor, for the right prostate lobe, the left prostate lobe, and for both right and left prostate lobes. In 58.7% (182) of patients primary prostate tumor was identified in both right and left lobes.

Table 28 Distribution of Patients According to the Primary Prostate Tumor Location

Location of the primary prostate tumor	Region						Missing		Total (n=310)	
	Base		Mid		Apex					
	n	%	n	%	n	%	n	%	n	%
Right Prostate Lobe (n=72)	21	6.8%	26	8.4%	20	6.5%	27	8.7%	72	23.2%
Left Prostate Lobe (n=49)	11	3.5%	14	4.5%	8	2.6%	24	7.7%	49	15.8%
Both Right and Left Prostate Lobes (n=182)	167	53.9%	152	49.0%	116	37.4%	68	21.9%	182	58.7%
Missing (n=7)	7	2.3%	7	2.3%	7	2.3%	7	2.3%	7	2.3%

8.4.7 Histopathological size of the primary prostate tumor (cm)

The mean histopathological size of primary prostate tumour was 2.9 (±1.9) cm. [Table 29]

Table 29 Descriptive Statistics for the Histopathological Size of the Primary Prostate Tumor

Variable	Mean	Std Dev	Median	Minimum	Maximum	N
Histopathological Size of the Primary Prostate Tumor (cm)	2.9	1.9	3.0	0.1	8.0	95

8.4.8 Histopathological grading according to Gleason system

The mean histopathological grading score according to Gleason system was 7.1 (±1.1). [Table 30]

Table 30 Summary Statistics for Histopathological Grading According to Gleason System

Variable	Mean	Std Dev	Median	Minimum	Maximum	N
Histopathological Grading According to Gleason System	7.1	1.1	7.0	4.0	10.0	305

97.7% (303) of study participants had Gleason score ≥5, and 67.1% (208) of the patients had Gleason score between 7 and 10. [Table 31]

Table 31 Distribution of Patients According to Gleason Score

Gleason score	n	%
2-4	2	0.6%
5-6	95	30.6%
7-10	208	67.1%
Missing	5	1.6%
Total	310	100.0%

8.4.9 Patient distribution according to TNM staging

Table 32 depicts the patient distribution according to the TNM staging. 25.5% (79) of study participants had metastatic prostatic cancer, 55.2% (171) had locally advanced cancer (58 patients had T3N0M0 and 113 patients T1/T4N1M0) whereas for 19.3% (60) of the study participants the TNM staging data were either NX, MX or missing.

Table 32 Patient Distribution According to TNM Staging

Evaluation of the Primary Tumor (T)	n	%
T1	57	18.4%
T2a	36	11.6%
T2b	23	7.4%
T2c	31	10.0%
T3a	82	26.5%
T3b	51	16.5%
T4	23	7.4%
Missing	7	2.3%
Evaluation of the Regional Lymph Nodes (N)	**n**	**%**
NX	39	12.6%
N0	94	30.3%
N1	166	53.5%
Missing	11	3.5%
Evaluation of Distant Metastasis (M)	**n**	**%**
MX	13	4.2%
M0	197	63.5%
M1a	50	16.1%
M1b	20	6.5%
M1c	9	2.9%
Missing	21	6.8%

8.4.10 Evaluation of the histologic grade (G)

Table 33 Patient Distribution According to Histologic Grade (G)

Histologic Grade (G)	n	%
Gx	2	0.6%
G1	42	13.5%
G2	64	20.6%
G3-4	55	17.7%
Missing	147	47.4%
Total	310	100.0%

8.4.11 Vascular, lymphatic, and perineural invasion and sites of metastasis

In 47.4% (147) patients vascular and/or lymphatic and/or perineural invasion was recorded while in only 23.5% (73) of patients no invasion was observed. [Table 34]

Table 34 Distribution of Patients According to Vascular, Lymphatic and Perineural Invasion

Vascular, Lymphatic and Perineural Invasion	n	%
Vascular invasion	58	18.7%
Lymphatic invasion	40	12.9%
Perineural invasion	124	40.0%
None	73	23.5%
Missing	90	29.0%

Bones were the most frequent site of metastasis of prostate cancer recorded in 97.5% (77/79) of patients with metastatic disease. [Table 35]

Table 35 Distribution of Patients According to the Sites of Metastasis

Sites of Metastasis	n	%
Bones	77	24.8%
Lugs	10	3.2%
Liver	13	4.2%
Pleura	2	0.6%
Other	17	5.5%

8.5 Therapeutic management of prostate cancer

8.5.1 Prostate surgery (prostatectomy)

27.1% of the patients had undergone prostatectomy. [Figure 2]

Figure 2 Percentage of Patients Who Underwent Prostate Surgical Operation

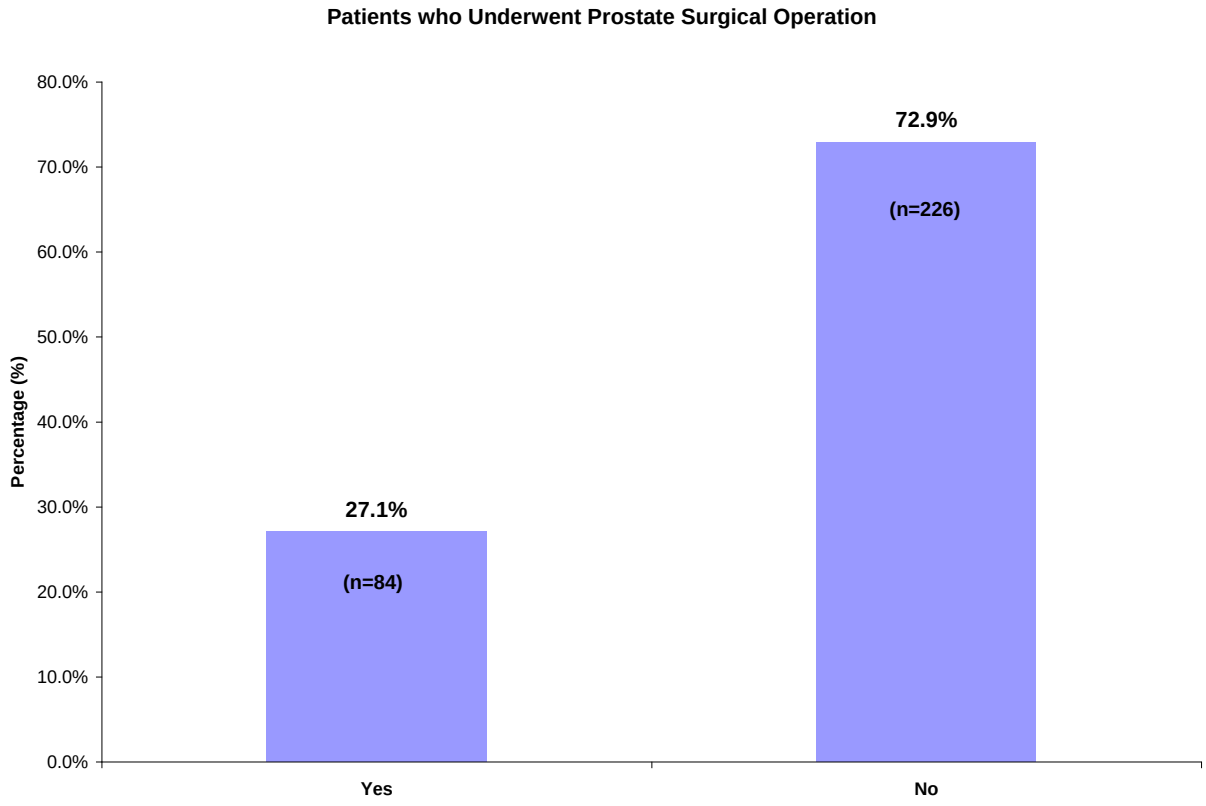


Table 36 presents the types of prostatectomy performed. Radical retropubic prostatectomy was the most frequent one performed by 90.5% (76) of patients that underwent surgical operation.

Table 36 Type of Prostatectomy

Type of Prostatectomy (n=84)	n	%
Radical retropubic prostatectomy	76	24.5%
Radical perineal prostatectomy	3	1.0%
Radical laparoscopic prostatectomy	0	0.0%
Other	1	0.3%
Missing	4	1.3%

In 75% (63/84) of patients underwent prostatectomy, pelvic lymph nodes resection was performed (20.3% of all study population). [Table 37]

Table 37 Pelvic Lymph Nodes Resection

Patients Who Underwent Prostate Surgical Operation (n=84)	n	%
Pelvic lymph nodes resection		
Yes	63	20.3%
No	13	4.2%
Missing	8	2.6%
Postoperative complications		
Yes	18	5.8%
No	63	20.3%
Missing	3	1.0%

21.4% (18/84) of patients underwent prostatectomy presented postoperative complications (5.8% of all study population). Urinary incontinence was the most frequent postoperative complication reported. [Table 38]

Table 38 Postoperative Complications

Complications in Patients who underwent Prostate Surgical Operation (n=84)	n	%
Infection	1	1.2%
Urinary incontinence*	9	10.7%
Bladder lithiasis	1	1.2%
Haematuria	1	1.2%
Surgical bleeding	2	2.4%
Urethral stricture	2	2.4%
Erectile dysfunction*	4	4.8%
Missing	2	2.4%

* 4 patients had both Urinary incontinence and erectile dysfunction

8.5.2 Radiotherapy

Only 57 (18.4%) of the patients received radiation therapy. [Figure 3]

Figure 3 Percentage of Patients who Received Radiation Therapy

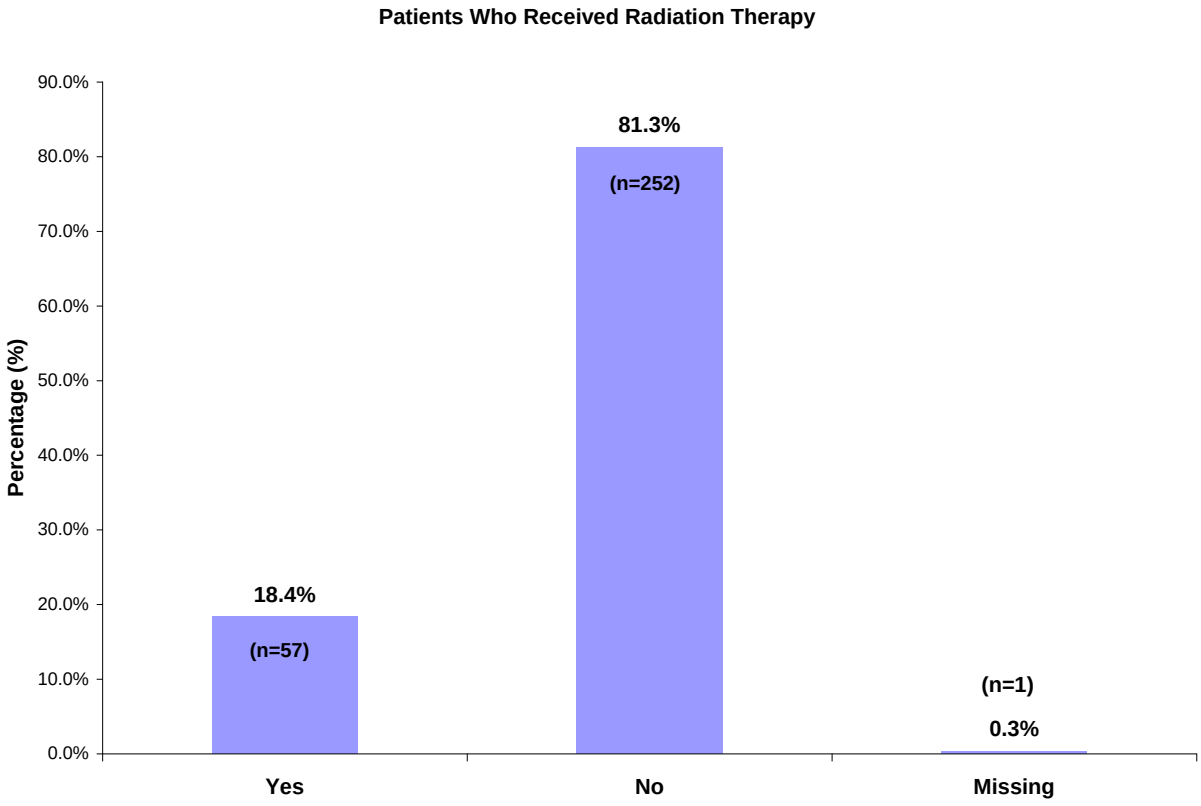


Table 39 presents the type of radiotherapy received, with the 3D-CRT being the most frequently recorded in 47.4% (27) of the patients treated with radiotherapy (8.7% of total study population).

Table 39 Distribution of Patients According to the Type of Radiotherapy

Type of Radiotherapy Received (n=57)	n	%
3D-CRT	27	8.7%
IMRT	9	2.9%
2D-CRT	7	2.3%
HDR monotherapy	3	1.0%
HDR in combination with EBRT	3	1.0%
LDR monotherapy	0	0.0%
LDR in combination with EBRT	0	0.0%
Missing	8	2.6%

In total, 35% (20/57) of patients treated with radiotherapy presented post-radiotherapy complications with diarrhea being the most frequently reported. [Table 40]

Table 40 Post-Radiotherapy Complications

Complications in Patients who received Radiotherapy (n=57)	n	%
Diarrhea	7	12.3%
Radiation cystitis	5	8.8%
Radiation enteritis	4	7.0%
Frequent urination	3	5.3%
Frequent urination	2	3.5%
Radiation colitis	2	3.5%
Hematuria	1	1.8%
Anaemia	1	1.8%
Rectal bleeding	1	1.8%
Lower limb swelling	1	1.8%

8.5.3 Topical therapy

Only 3 (0.97%) patients received topical therapy. [Figure 4]

Figure 4 Percentage of Patients who Received Topical Therapy

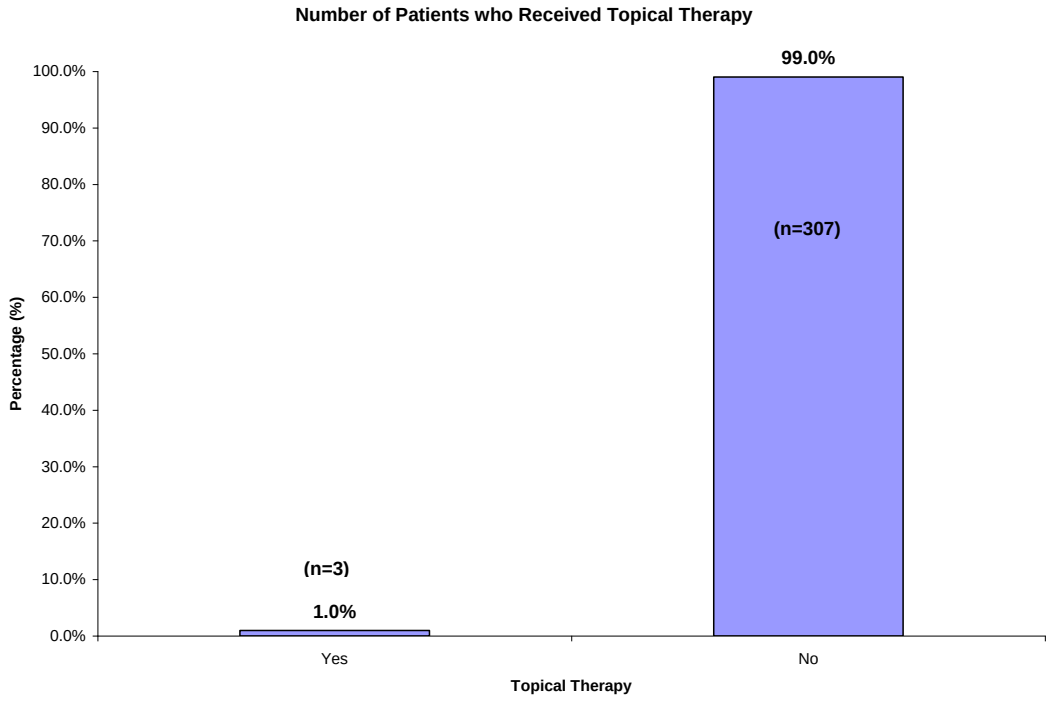


Table 41 Type of Topical Therapy and Post-Therapy Complications

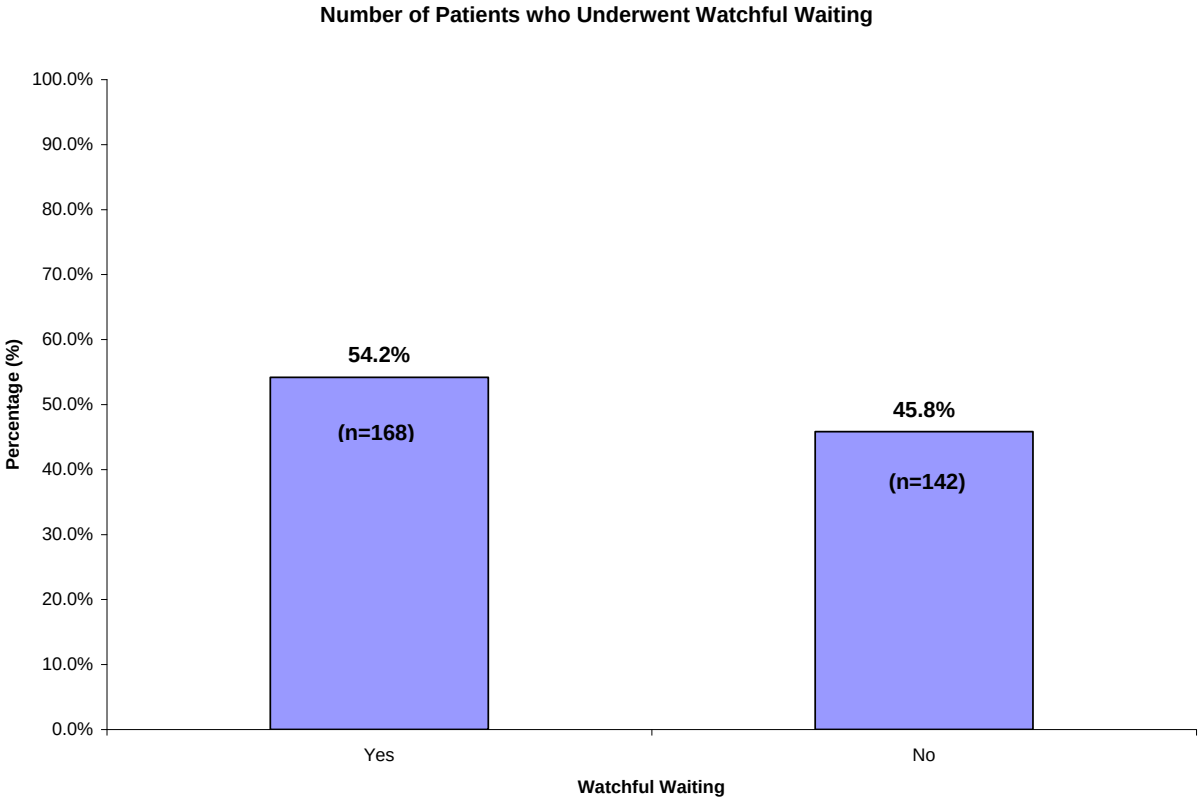
Type of Topical Therapy (n=3)	n	%
RITA	2	0.6%
Cryosurgical ablation	1	0.3%
HIFU	0	0.0%

No post-topical therapy complications were reported.

8.5.4 Watchful waiting

54.2% (168) of the study participants underwent watchful waiting. [Figure 5]

Figure 5 Percentage of Patients who Underwent Watchful Waiting



Tables 42 and 43 present the frequency of patient follow-up evaluation as well as of PSA testing. Follow-up frequency for most of the patients who underwent watchful waiting (71.4%) was every three (3) months, and so was for the PSA testing (78.6%).

Table 42 Frequency of Patient Follow-up

Frequency of Patient Follow-up (months)	n	%
1	10	3.2%
1.5	1	0.3%
2	12	3.9%
3	120	38.7%
6	25	8.1%

Table 43 Frequency of PSA Testing

Frequency of PSA Testing (months)	n	%
1	2	0.6%
1.5	1	0.3%
2	10	3.2%
3	132	42.6%
4	3	1.0%
5	1	0.3%
6	18	5.8%

8.5.5 Hormone therapy

Almost all patients (99.7%) received hormone therapy. [Table 44]

Table 44 Percentage of Patients who Received Hormone Treatment

Patients who Received Hormone Treatment			
Yes		No	
n	%	n	%
309	99.7%	1	0.3%

The types of hormone treatment administered are presented in detail in Table 45. Most of study participants (89.7%) underwent complete androgen blockade (CAB) combining anti-androgens with LHRH agonists or orchiectomy.

Table 45 Type of Hormone Treatment Administered

Type of Hormone Treatment Administered	n	%
Testosterone- lowering treatment as monotherapy	**4**	**1.3%**
Bilateral orchiectomy	0	0.0%
Estrogens	0	0.0%
LHRH agonists	4	1.3%
LHRH antagonists	0	0.0%
Antiandrogens as monotherapy	**27**	**8.7%**
Steroidal antiandrogens	0	0.0%
Non-steroidal antiandrogens	27	8.7%
Combination therapy	**278**	**89.7%**
Complete androgen blockade (CAB)	278	89.7%
LHRH agonist + antiandrogen	*268*	*86.5%*
LHRH agonist + antiandrogen + estrogen	*6*	*1.9%*
Antiandrogen + estrogen	*2*	*0.6%*
Bilateral orchiectomy + LHRH agonist + antiandrogen	*1*	*0.3%*
Bilateral orchiectomy + antiandrogen	*1*	*0.3%*
Peripheral androgen blockade (PAB)	0	0.0%

The mean time from diagnosis to hormone therapy commencement was 3.1 (±8.9) months. [Table 46]

Table 46 Time from Diagnosis to Hormone Therapy Commencement

Variable	Mean	Std Dev	Median	Minimum	Maximum	N
Time from diagnosis to hormone therapy commencement (in months)	3.1	8.9	0.5	0.0	58.9	221

27 patients discontinued hormone therapy due to completion of the therapy. Only 1 patient discontinued due to AE, 6 patients due to disease progression, and 14 patients for other reasons. [Table 47]

Table 47 Discontinuation of Hormone Therapy and Reasons for Discontinuation

Discontinuation of Hormone Therapy and Reasons for Discontinuation	n	%
Completion of therapy	27	8.7%
Adverse event occurrence	1	0.3%
Lost to follow-up	1	0.3%
Disease progression	6	1.9%
Other	14	4.5%
Death	*2*	*0.6%*
Intermittent androgen blockade	*2*	*0.6%*
Low PSA level	*2*	*0.6%*
Prostatectomy	*2*	*0.6%*
Radiotherapy initiation	*4*	*1.3%*
Resistance to therapy	*2*	*0.6%*

8.5.6 Chemotherapy and biological therapy

6 out of 310 (1.9%) patients received chemotherapy, while none of them underwent biological therapy. [Table 48]

Table 48 Percentage of Patients who Received Chemotherapy or Biological Therapy

Other Therapies	n	%
Chemotherapy	6	1.9%
Biological therapy	0	0.0%

9 EVALUATION OF SAFETY DATA

No safety data were collected in the present study.

10 REFERENCES

1. Parker, S.L., et al., Cancer statistics, 1997. CA Cancer J Clin, 1997. 47(1): p. 5-27

2. Boyle, P., G. Severi, and G.G. Giles, The epidemiology of prostate cancer. Urol Clin North Am, 2003. 30(2): p. 209-17.