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MANAGEMENT OF HORMONE REFRACTORY PROSTATE CANCER

Diploma thesis

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I dedicate this work to my Parents

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LIST OF ABREVIATIONS

AA	Abiraterone Acetate
ADT	Androgen deprivation treatment
AIPCa	Androgen insensitive prostate cancer
AR	Androgen receptor
AUA	American Urology Association
CAB	Complete androgen blockade
CHT	Chemotherapy
CRPCa	Castrate resistant prostate cancer
CT	Computer tomography
CYP17A1	Cytochrome P 17A1
DHT	Dehydrotestosterone
DHEA	Dehydroepiandrosterone
EUA	European Urology Association
GnRH	Gonadotropin-releasing hormone
GRP	Gastrin releasing peptide
GS	Gleason score
HT	Hormonal therapy
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HRPCa	Hormone refractory prostate cancer
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
IL	Interleukin
LBD	Ligand binding domain

LH	Luteinizing hormone
LHRH	luteinizing hormone-releasing hormone
LNCaP	Lymph Node Carcinoma of the Prostate
MAB	Maximum androgen blockade
MRI	Magnetic resonance
NSAA	non-steroidal anti-androgen
PCa	Prostate cancer
PCWG2	Prostate Cancer Working Group
PSA	Prostate specific antigen
QoL	Quality of life
RT	Radiation therapy
SD	Standard deviation
TNM	Tumour, lymph nodes and metastasis
TAA	tumour- associated antigens
TURP	Transurethral Resection of the Prostate

ABSTRACT

Background: In the last decade, there has been tremendous breakthroughs in the management of hormone refractory prostate cancer (HRPCa). Although new agents have shown promising results, there are still challenges that meet the doctor in the daily management of this type of cancer.

Objective: the aim of this research is to assess the effectiveness of the current treatment by analysing the refractory status of the patients, the PSA level curve during treatment, the occurrence of medical side effects and the prognostic factors. Furthermore, to assess the compliance of the patients and any correlations between the above-mentioned criteria.

Materials and Methods: In this retrospective study, random patients' files were studied and 46 patients that met the criteria of HRPCA were included in the study. Their age, cancer stage, and PSA values were taken into account. A phone interview was conducted to evaluate their treatment satisfaction and presence or absence of treatment's side effects.

Results: The study population had a median age of 74 years (SD ± 5.5). The refractory status occurred at a median time of 1.5 years (SD ± 2) or 19 months. The median value of PSA during treatment was 16 ng/ml (SD ± 36), with values ranging from 2-161 ng/ml. The most common side effect was the presence of hot flashes (67.4%), followed by urinary retention and weakness (58.7%) and the third place was attributed to back pain (45.7%). From the patients that exhibited side effects, 78.3% stated to have not received any treatment for the side effects compared to 21.7% that have received some type of treatment. Patients with decreased or resolved side effects show a significant satisfaction at $p<0.001$. There is a significant correlation between the patient regular trimestral visits and their satisfaction of the overall treatment $p= 0.03$. The correlation between tumour stages and Gleason score shows a statistical significance at stage III and IV, $p=0.02$ and $P=0.04$ respectively. In the evaluation of PSA level as a prognostic factor, 65.2 % of patients have a mean PSA value of ≥ 10 ng/ml, thus having a poor prognosis compared to 23.9 % with PSA between 4-10 ng/ml, having a good prognosis and 10.9 % with PSA ≤ 4 ng/ml thus having the best prognosis, $p < 0.01$.

Conclusion: The refractory status found at 1.5 years more or less correspond to what other similar research has published. There was a statistical significant association between the PSA values and treatment response. This will help predict the disease course in such a way that each patient can receive an appropriate and individualized treatment. Although the majority of patients stated that they had not received any treatment for the side effects, regular trimestral visit gave a higher satisfactory response from these patients.

KOPSAVILKUMS

Aktualitāte. Pēdējās desmitgades laikā būtiski mainījusies pieeja hormonrefraktāra (HRPV) prostatas vēža terapijā. Kaut arī atrasti jauni preparāti HRPV ārstēšanā, vēl joprojām urologi ikdienas praksē sastopas ar daudzām neskaidrībām pie šīs prostatas vēža formas.

Darba uzdevums. Analizēt pacienta stāvokli pie hormonālās refraktaritātes, PSA izmaiņas terapijas laikā, hormonālās terapijas blakus efektus, kā arī slimības prognostiskos faktorus, kā arī pacientu atbilstību konkrētajai terapijai un korelāciju starp visiem augstāk minētajiem parametriem.

Materiāls un metodes. Retrospektīvā pētījumā tika iekļauti 46 pacienti, kas atbilda HRPV kritērijiem. Tika analizēts šo pacientu vecums, prostatas vēža stadija un PSA līmenis. Telefona intervijā tika aptaujāts šo pacientu apmierinātība ar terapiju un patreizējās terapijas blakus efekti.

Rezultāti. Pētījuma pacientu vidējais vecums bija 74 gadi (SD +5,5). Vidējais laiks līdz hormonālai refraktaritātei bija 1,5 gadi (SD +2) jeb 19 mēneši. Ārstēšanas gaitā vidējais PSA bija 16 ng/dl (SD+36) ar PSA rādījumiem no 2-161 ng/dl. Visbiežākie terapijas blakus efekti bija karstuma viļņi (67,4%), kā arī urīna aizture un vājums (58,7%). 45,7% gadījumos tika atzīmētas kaulu sāpes. Pacientiem ar terapijas blakus efektiem 78,3% nepielietoja nekādu terapiju blakus efektu mazināšanai, pretēji 21,7%, kas pielietoja terapijas blakus efektus mazinošu terapiju. Pastāv statistiski nozīmīga korelācija starp regulārām ik 3 mēnešu vizītēm un viņu kopējo apmierinātību ar terapiju (p=0,03). Korelācija starp prostatas vēža stadiju un Gleason rādītāju norāda uz sliktāku prognozi 3. un 4. stadijā, attiecīgi p=0,02 un 0,04. Analizējot PSA kā slimības prognostisko faktoru secināts, ka 65,2% pacientiem vidējais PSA bija >10, kas liecina par prognostiski sliktu slimības gaitu, salīdzinot ar 23,9% pacientiem ar PSA 4-10. Vislabākā prognoze tika novērota 10,9% pacientiem ar PSA <4 ng/ml (p<0,01).

Secinājumi. Atbilstoši literatūras datiem, prostatas vēža slimniekiem, pielietojot hormonālo terapiju, hormonālā refraktaritāte iestājas vidēji 1,5 gadu laikā. Analizējot statistiski nozīmīgu PSA līmeni un terapijas gaitu ļauj secināt, ka katram pacientam tiek pielietota individualizēta un atbilstoša hormonālā terapija. Kaut arī vairums HRPV pacientu atzīmēja.ka nav pielietojuši hormonālās terpijas blakus efektu ārstēšanu, regulāras ik 3 mēnēšu vizītes pie urologa ir svarīgas.

RÉSUMÉ

Contexte : Il y a eu des avancées considérables dans le maniement de l'hormone réfractaire du cancer de la prostate dans la dernière décennie. Bien que les nouveaux éléments aient montré des résultats prometteurs, il y a encore des défis que rencontre le médecin dans la gestion quotidienne de ce type de cancer.

Objectif : Le but de cette recherche est d'évaluer l'efficacité du traitement actuel en analysant l'état réfractaire des patients, la courbe du taux de l'antigène spécifique de la prostate(ASP) au cours du traitement, l'apparition d'effets médicaux secondaires et les facteurs pronostics. En outre, il s'agit d'évaluer la conformité des patients et des corrélations entre les critères mentionnés ci-dessus.

Matériels et méthodes : Dans cette étude rétrospective, des dossiers des patients tirés au hasard ont été étudiés et 46 patients qui répondaient aux critères de l'hormone réfractaire du cancer de la prostate ont été retenus. Leur âge, le stade du cancer ainsi que les valeurs de l'ASP ont été pris en compte. De plus, une interview téléphonique a été menée afin d'évaluer leur satisfaction du traitement ainsi que de la présence ou l'absence d'effets secondaires au traitement.

Résultats : La population de l'étude comprenait 46 patients avec un âge moyen de 74 ans (SD ± 5.5). L'état réfractaire est survenu à une période moyenne de 1,5 ans (SD ± 2) ou 19 mois. La valeur moyenne de l'ASP pendant le traitement était à 16 ng/ml (SD ± 36), avec des valeurs allant de 2 à 161 ng/ml. Les effets indésirables les plus courants étaient la présence de bouffées de chaleur (67,4%). Suivit par la rétention urinaire et la faiblesse (58,7%) et à la troisième place, les douleurs dorsales (45,7%). De ces patients qui présentent des effets secondaires, 78,3% ont déclaré ne pas avoir reçu de traitement pour les effets secondaires et seulement 21,7% ont reçu un certain type de traitement. Les patients avec des effets secondaires diminués ou réglés montrent une satisfaction significative à $p < 0,001$. Il existe une corrélation significative entre les visites trimestrielles régulières des patients et leur satisfaction du traitement, $p=0,03$. La corrélation entre les phases de la tumeur et le taux de Gleason montre une signification statistique au stade III et IV, avec respectivement $p=0,02$ et $p=0,04$. Dans l'évaluation du niveau de l'ASP comme un facteur pronostic, 65,2% des patients ayant une valeur moyenne de ≥10ng/ml de ASP, avaient un mauvais pronostic, par rapport à 23,9% des patients avec un ASP entre 4 et 10ng/ml ayant un bon pronostic, et 10,9% avec un ASP de ≤ 4ng/ml ayant ainsi le meilleur pronostic $p<0,01$.

Conclusion : L'état réfractaire trouvé à 1,5 années correspond plus ou moins à ce que d'autres recherches similaires ont publié. Il y a une association statistiquement significative entre les

valeurs de PSA et la réponse au traitement. Cela peut aider à prédire l'évolution de la maladie d'une manière telle que chaque patient peut recevoir un traitement approprié et individualisé. Bien que la majorité des patients ont déclaré qu'ils n’avaient reçu aucun traitement pour les effets secondaires, les patients ayant bénéficié d'une visite régulière trimestrielle ont donné une réponse beaucoup plus satisfaisante.

1 INTRODUCTION

Prostate cancer is classified as the most common male malignant neoplasm and the second leading cause of cancer related death in the male pollution worldwide (Cookson, AUA 2014). In Latvia, it is the second most common malignancy in men after lung cancer. 961 cases were registered in 2013 (Central Statistical Bureau of Latvia, 2013).

This cancer predominantly affects men of old age with a median age of 72 years old at diagnosis.

In the last years, there has been a tremendous breakthrough in the development of a new approach in the management of advanced prostate cancer. Numerous new agents were introduced for the treatment and some are showing promising results.

Androgen deprivation therapy (ADT) is still the standard systemic treatment used for locally advanced or metastatic PCa. Approximately 80% of patients treated with ADT, which suppress testicular androgen production (surgical castration or administration of LHRH super agonists), or antagonists, which block AR by treatment show clinical and biochemical (decrease in serum PSA) evidence of improvement.

Although a good number of this cancer responds well to treatment, most of them progress into advanced stage with or without metastasis.

Over the years advance prostate cancer has bared different names including Hormonal Resistant or Refractory Prostate Cancer (HRPCa), Androgen Insensitive Prostate Cancer (AIPCa), and Castrate Recurrent PCa. Most recently, the term Castrate Resistant PCa has been commonly used.

For a cancer to be classified as advanced there should be evidence of disease progression such as aggravation of urinary tract symptoms, new clinical metastasis or progression of existing metastasis. In case of hormone refractory prostate cancer, there should be evidence of an increase of Prostate Specific Antigen (PSA) level in the patient during or after the treatment.

The exact mechanism of transition from castrate sensitive (primary cancer) to castrate resistant prostate cancer is still not fully understood. Nevertheless, with resent scientific research breakthrough, we now know that the androgen receptor plays a greater role in the progression of the cancer. Thus, novel treatments are made specifically for targeting these receptors in any level of their formation, sensitization and function.

Compared with castrate-sensitive prostate cancer, the prognosis for patients with Castrate Resistant Prostate Cancer (CRPC) is poor and survival is reduced. Treatment options have until very recently, been limited mainly to symptomatic relief of bone metastases, which are more common in CRPC than in castration-sensitive disease. Patient with CRPC demonstrate poor prognosis associated with a deterioration of quality of life (QoL). Most of these patients die with the disease due to their advanced age and life aged comorbidities.

1.1 AIM OF STUDY

The aim of this research is to assess the effectiveness of the current treatment by:

- Analysing the refractory status or the period from the beginning of the first hormonal treatment until the patients become refractory or resistant
- Analysing the PSA level fluctuation during treatment,
- Analysing the occurrence of medical side effects
- Assessing the compliance of the patients.
- Analysing the prognostic factors and any correlations between the above-mentioned criteria.

2 LITTERATURE REVIEW

2.1 DEFINITION

Castration-resistant prostate cancer (CRPC) is an advanced form of prostate cancer characterized by disease progression following surgical or pharmaceutical (androgen deprivation) castration. It is clinically defined as a failure of castration to prevent an increase in circulating hormones, which are associated with worsening prostate cancer. Over the last decade, there has been different definition made to identify HRPCa.

The recently published European Association of Urology (EAU, 2008) guidelines aim to standardize CRPC diagnosis, and includes a list of five defining factors of CRPC. These are:

- Serum castration levels of testosterone.
- Three consecutive rises of PSA two weeks apart, resulting in two 50% increases over the lowest level.
- Anti-androgen withdrawal for at least 4 weeks.
- PSA progression despite secondary hormonal manipulations
- Progression of osseous or soft tissue lesions: metastatic lesion of bone and surrounding soft tissue, showing the progression of the PCa.

Thus, Hormone-refractory / castrate resistant prostate cancer is defined as 2-3 consecutive rises in PSA levels obtained at intervals of greater than 2 weeks.

Other definitions have been formulated by the Prostate Cancer Clinical Trials Working Group (PCWG2) as a serum PSA greater than 2 ng/ml above the nadir and rising over one month with or without documented disease progression based on findings from CT scan and/or bone scan, bone pain, or obstructive voiding symptoms (Scher HI et al., 2007).

Traditionally, “advanced” prostate cancer was defined as a disease that had widely metastasized beyond the prostate, the surrounding tissue and the pelvic lymph nodes. It was also considered incurable by most clinicians, but currently, it has been shown that a cancer can be localized and still be advanced depending on the histological findings at diagnosis. For this fact, a high risk localized disease and PSA recurrence are the most common presentations of advanced prostate cancer.

The commonly encountered disease categories of advanced prostate cancer beside hormone refractory are summarized below. They range from prostate cancer that is confined to the prostate gland to prostate cancer that has spread outside of the prostate to the lymph nodes and bone.

- ***Locally Advanced Prostate Cancer:*** Cancer that has grown to fill the prostate or has grown through the prostate and may extend into the glands that help produce semen (seminal vesicles).
- ***Metastatic Prostate Cancer:*** Cancer that has spread (metastasized) to the bone, lymph nodes or other parts of the body. Through the depletion of the male sex hormone, testosterone or medications, improvement in the patient's urinary function and pain control can be achieved.

As by the definition HRPCa reoccurs after hormone (ADT) treatment, there are few of these cancers that are hormone insensitive right from the beginning of the treatment. This is because the PSA does not decrease despite the treatment. They are called primary hormone refractory PCa.

2.2 EPIDEMIOLOGY

The prevalence and incidence of prostate cancer in Latvia are increasing yearly. The prevalence ranges from 1813 cases in 2000 to 4850 cases in 2010 and the incidence ranges from 522 cases in 2000 to 855 cases in 2010, respectively (Ābel 2011).

The incidence of prostate cancer varies worldwide, with the highest rates found in the United States, Canada, and Scandinavia, and the lowest rates found in China and other parts of Asia. These differences could be due to a genetic susceptibility, exposure to unknown external risk factors, differences in health care and cancer registration, or even a combination of these factors.

In Europe, the incidence rate of prostate cancer is 214 cases per 1000 men, outnumbering lung and colorectal cancer. In a global survey, prostate cancer was among the three most common cancers diagnosed in men across 184 countries, with a lower prevalence in underdeveloped countries likely because of delayed diagnosis and perhaps also because of their kind of nutrition. Prostate cancer prevalence has increased primarily because of the increased use of prostate-

specific antigen (PSA) testing: PSA detection is responsible for earlier diagnosis by up to 12.3 years and has led to an increase in early-stage diagnosis.

Published information on the frequency and characteristics of CRPC patients are lacking (Hirst, 2012). The median survival duration in men with castrate-resistant prostate cancer (CRPC) is 2 to 3 years, although this may improve with newer therapies.

The mortality also varies worldwide, with the highest rates reported in the Caribbean, Baltic region (Estonia, Latvia and Lithuania) in Scandinavia (Denmark, Norway and Sweden) and the lowest rates in China, Japan, central and southern Europe. This reflects a real increase in risk factors. In the USA, prostate cancer mortality has fallen substantially in spite of the marked increase in diagnosis due to early detection.

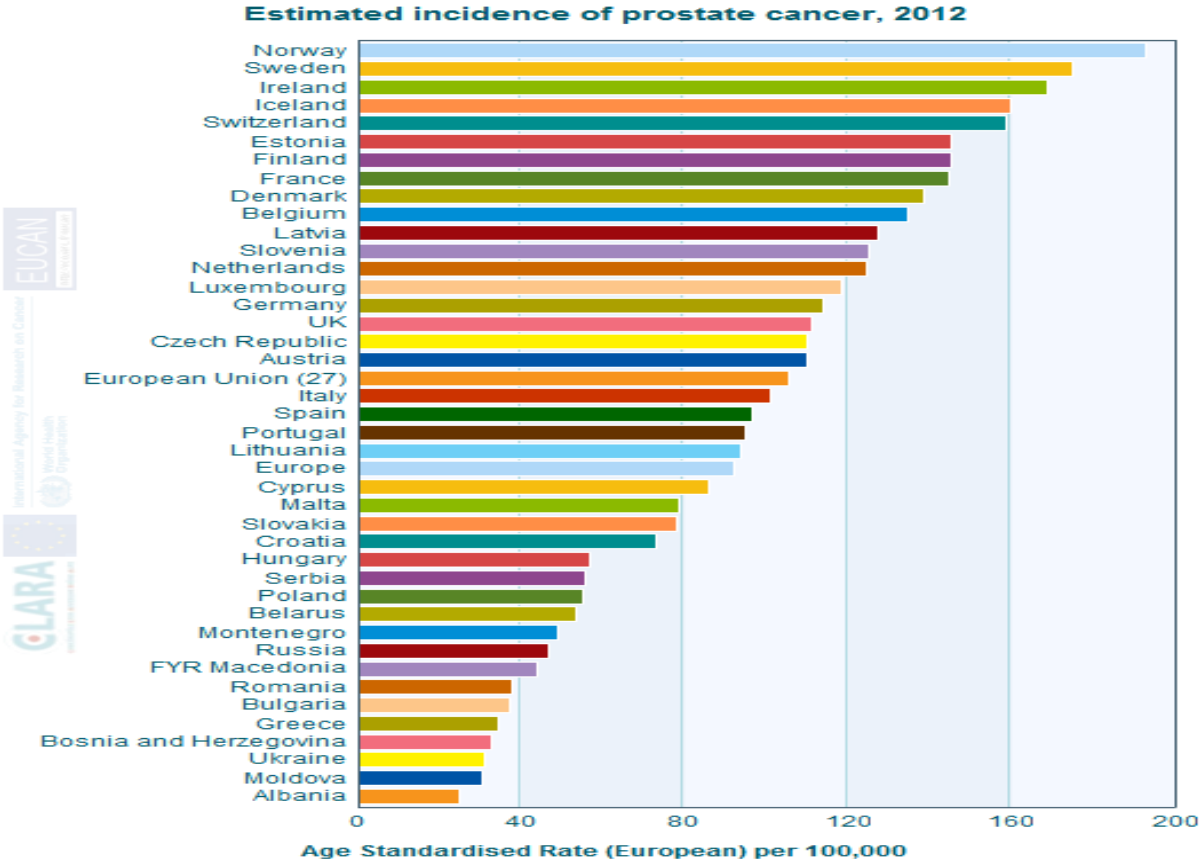

Figure 1. Age-standardized prostate cancer incidence and mortality rate by country (year 2012 estimates)

2.3 RISK FACTORS

The risk of developing advance HRPCa is associated with advancing age, ethnicity, a positive family history, and may be influenced by diet and other factors.

2.3.1 Age and ethnicity

Aging is the major non-changeable risk factor in HRPCa. In the United States, 70% of all cases of prostate cancer are diagnosed in men over 65 years old. It is relatively rare for prostate cancer to be diagnosed in men under 50 years of age, but after this age, the incidence and mortality rates increase exponentially. Carter et al showed that 20% of men aged 50 to 60 years and 50% of those aged 70 to 80 years had histologic evidence of malignancy. It has been estimated that a 50-year-old man has a lifetime risk of 42% for developing histologic evidence of prostate cancer, a 9.5% risk of developing clinical disease, and a 2.9% risk of dying of prostate cancer (Carter et al., 1990). African Americans have among the highest rates of prostate cancer in the world (275.3 per 100,000 men). Nearly 60% higher than among whites (172.9 per 100,000), which, in turn, is higher than the rates for Hispanics (127.6 per 100,000) and Asians/Pacific Islanders (107.2 per 100,000).

2.3.2 Family history and genetic susceptibility

The risk of developing prostate cancer doubles for men who have a father or brother affected by prostate cancer, and risk increases further when multiple first-degree relatives are affected.

Epidemiologic studies indicate that men with a positive family history are diagnosed at an earlier age, on average 6 to 7 years earlier than those without affected first-degree relatives (Crawford, David E, 2003). The familial clustering of prostate cancer may be caused by inheritance of a susceptibility gene, but it may also be caused by exposure to common environmental factors.

2.3.3 Diet and environment

The Western lifestyle, particularly the higher intake of fat, meat, and dairy products, may be responsible for conveying higher prostate cancer risk. Beef and dairy products are major sources of dietary branched fatty acids. An enzyme that plays a key role in the peroxisomal oxidation of these fatty acids is upregulated in prostate cancer but not in the healthy prostate. The

oxidation process generates hydrogen peroxide, which may be a source of carcinogenic oxidative damage to the prostate genome.

Because a high-fat diet is linked with a higher incidence of prostate cancer, a low-fat diet may be beneficial for patients at high risk of developing prostate cancer (namely those with positive family history, African American males) and for patients undergoing treatment for advanced prostate cancer. Tomatoes, broccoli, green tea, soy, lycopene, licorice root, selenium, and antioxidants have all been hypothesized to be beneficial (Kirsh VA et al, 2006; Kavanaugh CJ et al, 2007).

The lower incidence of prostate cancer in Japan than in the United States may be related to the difference in intake of soybean products that are rich in isoflavones, such as genistin and daidzin. Experimental studies suggest that these isoflavones can inhibit protein tyrosine kinases that are important in cell proliferation and transformation, as well as in angiogenesis, and thereby limit the development and metastasis of prostate tumours (Crawford, David E, 2003).

2.4 PATHOGENESIS

2.4.1 Action of testosterone

The prostate is an androgen-regulated organ of the male population and needs androgens for development, growth and function.

Testosterone and 5a-dihydrotestosterone (DHT) are the principal androgens. Testosterone is the principal circulating androgen secreted by the testis and its synthesis is regulated by the action of luteinizing hormone (LH) on the Leydig cells of the testis. Production of testosterone is stimulated by the hypothalamus through luteinizing hormone releasing hormone (LHRH), which activates the pituitary gland to produce luteinizing hormone (LH), which in turn stimulates the Leydig cells. A small proportion (5-10 %) of testosterone is produced by the adrenal glands. In addition, there is a negative feedback loop where testosterone inhibits the release of LHRH in order to maintain the circulating testosterone within normal levels.

Although the testes secrete small quantities of DHT, much of the circulating DHT is formed in peripheral tissues by the action of two 5a-reductase (see *figure 2*). Both testosterone and DHT bind to the same androgen receptor protein with high affinity and activate it. This induces a conformational change in the receptor structure that leads to dissociation of chaperone proteins, which normally binds to the inactivated Androgen receptor (AR).

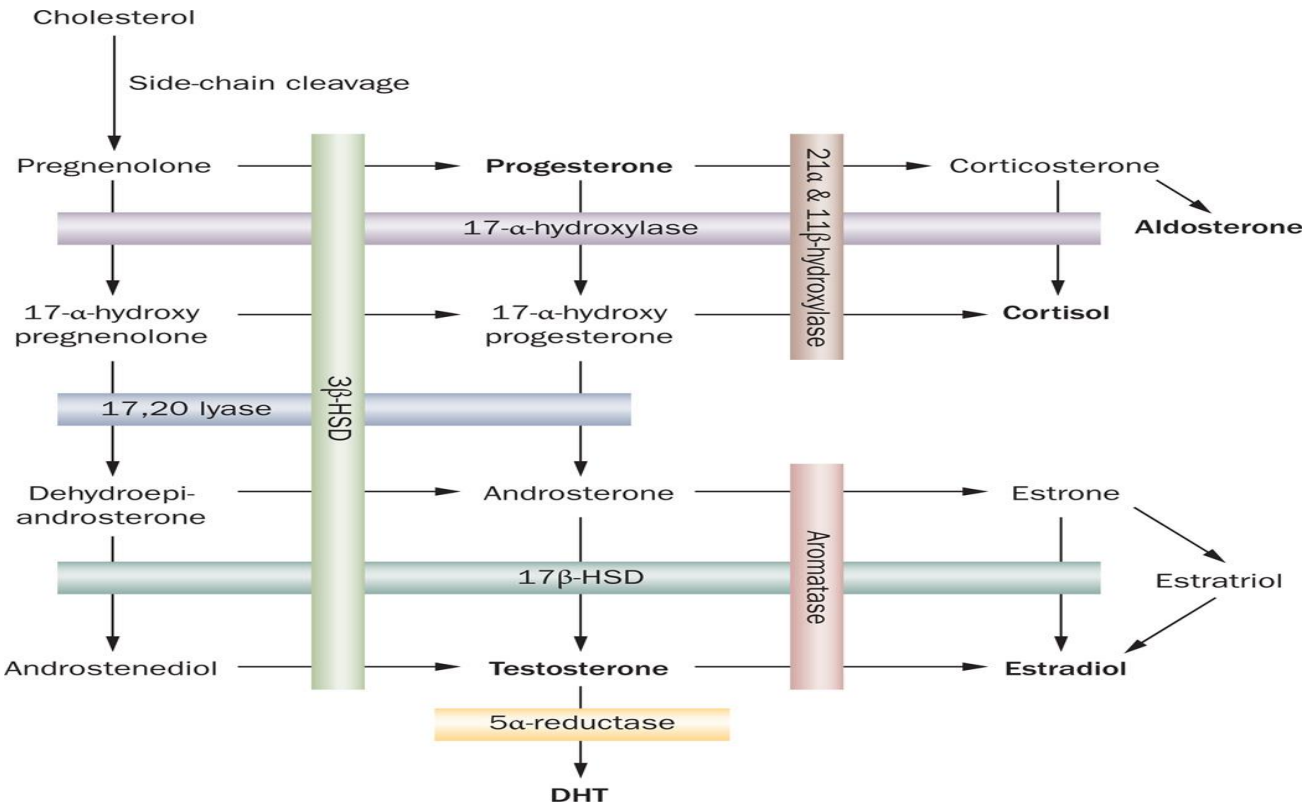

Figure 2*. Interrelations and interconversions among androgens. The common precursor cholesterol is sequentially modified by the enzymes to synthesize the steroid hormones. Testosterone is converted to its more potent form, DHT, by the 5α-reductase enzymes. Abbreviations: DHT, dihydrotestosterone; HSD, hydroxysteroid dehydrogenase.*

During androgen-independent progression, prostate cancer cells develop a variety of cellular pathways to survive and flourish in an androgen-depleted environment. These include AR gene amplification, AR gene mutations, involvement of co-regulators, ligand-independent activation of the androgen receptor, and intra-tumoral androgen synthesis.

2.4.2 The AR role in HRPCa

The major role of AR in normal prostate is to drive the differentiation of luminal epithelial cells and regulate the transcription of protein products that are required for prostate function, such as PSA. The critical functions of AR in prostate cancer have been less clear, but are thought to stimulate the expression of a series of genes that regulate cell cycle that are required for cancer survival or growth. The AR is pivotal not only to the initiation and growth of prostate cancers, but also in their responses to therapy.

The molecular events that drive the transition from an androgen-dependent to androgen-independent state remain unclear. It is unknown whether androgen-dependent cells acquire the ability to proliferate in castrate levels of androgen, or if castrate levels of androgen somewhat causes the outgrowth of a minor population of tumour cells that are androgen-independent. Immunohistochemical analyses have shown that most androgen-independent tumours continue to express the AR and the AR responsive PSA protein.

2.4.2.1 Overexpression / amplification of AR

Amplification of the AR gene is a potent mechanism for increasing expression of the AR. Studies have found that approximately 25 to 30% of androgen-independent tumours that arise after hormonal therapy have AR amplification. The increase in receptor abundance results in sufficient ligand binding for sustained AR signalling in castrate levels of androgens (Saraon 2011). This is consistent with the reports that patients with AR gene amplification have disease recurrence while on therapy and have a greater likelihood to respond to second line hormonal therapy than patients without AR amplification have.

2.4.2.2 Androgen receptor mutation

Increased production of androgen receptor is likely secondary to gene amplification because of mutation. Mutation of the AR gene to either a hypersensitive receptor or a receptor with expanded ligand specificity would show androgen-independent properties. The frequency of AR mutations is rare in early the stages of tumorigenesis, but are more frequent in advanced or recurrent tumours (Saraon 2011).

2.4.2.3 Increased local production of androgen by prostate Cells

An increase in local production of highly active androgens most likely occurs by increased rate of conversion of testosterone to dihydrotestosterone by increasing 5α-reductase activity. Analysis of testosterone and dihydrotestosterone in serum and in prostate tumour samples of patients following androgen ablation therapy found that tumour samples had higher dihydrotestosterone levels than serum samples. This suggests that prostate cancer cells, by upregulating 5a-reductase, may more effectively convert testosterone to the highly active

dihydrotestosterone, thus producing sufficient localized hormone to promote AR signalling (Lucas P. N., 2011).

2.4.2.4 Activation of AR by growth factors and cytokines

Numerous studies indicate that the AR can be activated by interaction with non-steroid molecules. This is called promiscuous receptor activation (Saraon 2011). Growth factors that are ligands for receptor tyrosine kinases including epidermal growth factor, insulin-like growth factor and keratinocyte growth factor, can initiate a signalling cascade that culminates in AR activation. The androgen-independent signalling initiated by neuropeptides has been of particular interest since an increase of neuroendocrine cells, and an increase in neuroendocrine cell-derived soluble factors such as Gastrin releasing peptide (GRP), neurotensin, serotonin, Interleukin 8 (IL8), and Interleukin 6 (IL6), in prostate tissue, has been associated with androgen ablation therapy. Additionally, receptors for GRP, neurotensin and IL6 are present on prostate tumour derived cells. Thus, neuroendocrine molecules can serve as paracrine factors to stimulate tumour proliferation in an androgen-independent manner. IL6 and IL8 mediate inflammatory responses, suggesting that the immune system may play a role in prostate cancer. The latter mechanism underscores the potential importance of the tumour-microenvironment interaction in the development of androgen independence.

2.4.2.5 Altered expression of AR co-activators

Co-activators/co-regulators proteins enhance the activity of the androgen receptor to alternative ligands, thereby sensitizing the receptor to lower levels of native and non-native ligands, leading to ligand-independent activation. AR co-regulators can be broadly grouped as:

(1) Chaperone:. These proteins (including heat shock proteins) interact with newly translated AR to promote proper folding, cytoplasmic localization, AR stability and interaction with ligand.

(2) Histone and chromatin modifying proteins.

(3) Factors that bridge the transcriptional machinery to the AR.

2.4.3 Intra-turmoral androgen synthesis

Nishiyama and colleagues (2004) measured levels of dihydrotestosterone in patients treated with androgen deprivation therapy (castration flutamide). In those studies, the investigators found that the levels of prostatic dihydrotestosterone remained at approximately 25% following androgen deprivation therapy, compared to levels measured prior to androgen deprivation. By contrast, measurements examining serum levels of dihydrotestosterone in the same individuals demonstrated that DHT levels fell by over 90%.

Mostaghel et al (2007) examined intra-prostatic androgen levels and patterns of androgen regulated gene expression in normal men and in archival prostate cancer specimens following varying lengths of androgen deprivation therapy. The results of these experiments demonstrated that androgen-regulated gene expression persisted and were substantially reduced only in those subjects with the most profound suppression of intra-prostatic androgen levels. Finally, examination of the levels of androgen dependent gene expression in primary prostate cancers at different time, points of the androgen deprivation revealed evidence that the expression of androgen-regulated genes persisted in each of the time points examined.

2.5 DIAGNOSIS

2.5.1 Serum prostate specific antigen

Prostate specific antigen or PSA is a sensitive and specific serum marker for prostate tissue. Serial measurements are routinely obtained to detect early disease recurrence in men who have received definitive treatment for localized disease.

Monitoring PSA after definitive treatment of localized prostate cancer or during hormonal treatment (ADT) leads to the identification of localized advanced cancer. In this situation, signs or symptoms of recurrence or disseminated disease may also worsen. EAU guidelines (2007) recommend a trimestral monitory of PSA the first year of treatment, then a semestral monitoring starting from the second year of treatment or treatment free and once a year starting from the third year until the fifth year.

Patients with a PSA nadir $<$ 4 ng/ml need to be followed every six months by assessment of PSA levels, Whereas patients with PSA $>$ 4 ng/ml need to be followed every three months to discuss second-line hormone therapy or to recognise the transition to hormone-refractory PCa.

Patients with a prostate-specific antigen (PSA) value of 10ng/mL or higher are likely to progress to advanced cancer or refractory state.

2.5.2 Biopsy and histology

2.5.2.1 Transrectal ultrasonography (TRUS)

TRUS guided needle biopsy of the prostate is indicated for tissue diagnosis in patients who present with elevated prostate-specific antigen (PSA) levels on abnormal findings on digital rectal examination.

2.5.2.2 Grading

Under a microscope, the cell structure and microscopic attributes of the tissue sample are examined and are graded:

- Grade 1: Cells appear normal and are not growing rapidly.
- Grade 2: Cells appear slightly different from normal.
- Grade 3: Many abnormal cells are present but the majority is still normal
- Grade 4: very few normal cells
- Grade 5: All cells appear abnormal

The Gleason grading system is the most common classification used that helps to determine the histologic characteristics of prostate cancer. The sum of the most predominant grade and the second most common histologic pattern determines the Gleason score (GS). This scoring system assigns a number from two to 10 to describe how abnormal the cells appear under a microscope. It describes how different the cancer cells look from normal cells and how likely it is that the tumour will spread. The lower the number, the less likely the tumour is to spread. A score of 2 to 4 means the cells still look very much like normal cells and pose little danger of spreading quickly. A score of eight to 10 indicates that the cells have very few features of a normal cell and are likely to be aggressive. A score of five to seven indicates intermediate risk. Patients with a Gleason score of six or higher are likely to progress to advanced cancer (if they have not already done so).

2.5.3 Staging

The stage of the cancer is based on the results of the staging and diagnostic tests, including the prostate-specific antigen (PSA) test and the Gleason score. A high Gleason score is mostly associated with advanced cancer stage, thus showing a poor prognosis.

Prostate cancer is staged using the worldwide used TNM system. It separately assesses the tumour (T), lymph nodes (N) and secondary cancer or cancer dissemination to other organs (metastases – M).

Tumour staging is as follows:

- Stage T1-2c – Organ-confined disease, ***local prostate cancer***
- Stage T3a – Extra capsular extension of the tumour, ***locally advanced prostate cancer***
- Stage T3b – Invasion of the seminal vesicle(s), ***locally advanced prostate cancer***
- Stage T4 – Tumour fixed or tumour invading adjacent structures other than the seminal vesicles (e.g., the bladder neck, external sphincter, rectum, elevator muscles, and/or pelvic floor), ***advanced metastatic prostate cancer***

Lymph node involvement is staged as follow:

- Stage NX – Regional lymph nodes cannot be assessed
- Stage N0 – No regional lymph node metastasis
- Stage N1 – Regional lymph node(s) metastasis

Distant metastatic involvement staging consists of the following:

- Stage MX – Distant metastasis cannot be assessed
- Stage M0 – No distant metastasis
- Stage M1 – Distant metastasis
- Stage M1a – Distant metastasis other than regional lymph nodes
- Stage M1b – Metastasis to bone(s)
- Stage M1c – Other site(s)
- Stage pM1c – Metastasis to more than 1 site

2.5.3.1 Crawford and Blumenstein classification system

The definition of stage D by Whitmore-Jewett has been further stratified by Crawford and Blumenstein (Crawford, 2003). The additional stratification is thought to improve classification

and understanding of a subset of patients who have hormone-insensitive prostate cancer (Terris and al., 2015). It is as follows:

- Stage D1 – Involvement of pelvic lymph nodes
- Stage D1.5 – Rising prostate-specific antigen (PSA) level after failure of local therapy (i.e., biochemical failure)
- Stage D2 – Metastatic disease to bone and other organs
- Stage D2.5 – Rising PSA after nadir level
- Stage D3 – Hormone-refractory prostate cancer
- Stage D3.5 – Sensitive to hormones
- Stage D4 – Insensitive to hormones

2.5.4 Other tests

Different modalities are used to determine the stage of prostate cancer:

- **Chest radiography:** Chest radiography can be used as a baseline study or to help reveal rare pulmonary metastases in select cases
- **Abdominal Computer tomography (CT) scanning and Magnetic resonance (MRI)**: They may reveal extra capsular extension, seminal vesicle involvement, pelvic lymph node enlargement, liver metastases, and hydronephrosis (due to result of distal ureteral obstruction) in patients suspected of having locally advanced disease.
- **Pelvic lymphadenectomy**: A surgical procedure to remove the lymph nodes in the pelvis. A pathologist views the tissue under a microscope to look for cancer cells.
- **Seminal vesicle biopsy:** The removal of fluid from the seminal vesicles (glands that make semen) using a needle. A pathologist views the fluid under a microscope to look for cancer cells.
- **ProstaScint scan:** A procedure to check for cancer that has spread from the prostate to other parts of the body, such as the lymph nodes. A very small amount of radioactive material is injected into a vein and travels through the bloodstream. The radioactive material attaches to prostate cancer cells and is detected by a scanner. The radioactive material shows up as a bright spot on the picture in areas where there are many prostate cancer cells. ProstaScint scanning is used to reveal extra prostatic disease (i.e., localized recurrence or lymphatic spread). ProstaScint scans frequently

yield false-negative results, but the specificity of these studies may be improved when they are combined with CT scans or single-photon emission CT (SPECT) scanning.

- **Bone scintigraphy:** Those with a GS of greater than six and/or a PSA level of 20ng/ml or greater are candidates for a bone scan. A bone scan may be performed as a baseline for treatment response in patients with recurrent metastatic disease at high risk of having bony metastatic disease.

2.6 TREATMENT

The most common types of therapy for advanced prostate cancer and Hormone refractory prostate cancer according to types are described below:

2.6.1 Locally advanced PCa (T2c- T3 stages)

Localised prostate cancer, confined to the prostate gland. The principal management options are watchful waiting, prostatectomy and radiation therapy.

2.6.1.1 Watchful waiting and active surveillance

Watchful waiting and active surveillance are treatments used for patients who do not have signs or symptoms. These comprise closely monitoring of a patient's condition without giving any treatment until signs or symptoms appear or in case there are changes in test results. Treatment is given to relieve symptoms and improve quality of life.

In active surveillance, patients are given certain exams and tests, including digital rectal exam, PSA test and TRUS with or without transrectal needle biopsy to check if the cancer is growing.

2.6.1.2 Radical Prostatectomy

This can be done retro-pubically with an incision made in the abdominal wall or perineal, where an incision is made in the perineum.

Total removal of the prostate gland has been associated with erectile dysfunction and incontinence.

2.6.1.3 Radiation therapy

Radiation therapy (RT) can be given before or after prostatectomy. Side effects occur when the normal healthy cells near the treated area are exposed to the beam of radiation. Some side effects appear during the treatment, while others can develop afterwards. The most common side effects are those that develop during or shortly after the treatment. Some of these are:

- Urinary incontinence, increased frequency and urgency
- Change in bowel habits: increase frequency and urgency
- Discomfort at your back passage
- Skin changes: During radiotherapy, the skin on your bottom or between your legs may become sore and a bit darker. It may even look like sunburn.
- Fatigue (tiredness)
- Erectile dysfunction
- Infertility

2.6.1.4 Hormonal therapy /Androgen Deprivation Therapy (ADT)

Hormonal therapy aims to shrink the cancer and improve symptoms like poor urine flow.

These drugs can be taken orally, subcutaneously.

Anti-androgens can block the action of androgens (hormones that promote male sex characteristics). Sometimes a combination of the injections and tablets may be used. This is known as combination therapy or complete androgen blockade (CAB) or maximum androgen blockade (MAB).

Examples are flutamide, bicalutamide, enzalutamide, and nilutamide.

Drugs that can prevent the adrenal glands from making androgens include ketoconazole and aminoglutethimide.

The common side effects of hormone therapy include:

- Change in sexual function: erectile dysfunction, decrease libido
- Hot flushes
- Weight gain
- Fatigue
- Breast swelling and tenderness
- Osteoporosis

- Mood swings
- Depression
- Anaemia
- Memory loss

Types of Androgen Deprivation Therapy (ADT):

2.6.1.4.1 LHRH / GnRH Antagonists

This treatment option is often referred to as "medical orchiectomy" or "medical castration" because it is equivalent to the effect produced by orchiectomy (removal of the testicles). The important difference is that the medication can be stopped, so the effects are reversible.

In this treatment, the drug interferes with brains signals, and blocks the luteinizing hormone-releasing hormone activity. In other words, LHRH is blocked from stimulating production of luteinizing hormone (LH) and with no luteinizing hormone available, the testicles cannot produce testosterone. These drugs have an immediate onset of action leading to a fast and profound suppression of testosterone. These drugs do not produce the hormonal flare up seen often in the other ADT treatment. In other words, there is no short-term boost to testosterone production when a patient starts this therapy. Because of this risk, LHRH antagonists are used only for patients with advanced prostate cancer or who refuse any other type of hormone therapy due to preference or other side effects.

LHRH antagonists are injected through the buttocks or on the abdomen on a weekly basis for an entire month. After the first month, the patient receives the antagonist only once a month. Patients are strongly encouraged not to miss appointments, and to schedule those appointments as close to exactly four weeks later as they can.

The reduction in testosterone levels that occurs during GnRH antagonist therapy subsequently reduces the size of the prostate cancer. This in turn results in a reduction in prostate-specific antigen (PSA) levels in the patient's blood and so measuring PSA levels is a way to monitor how patients with prostate cancer are responding to treatment. After the first injection, patients should receive a blood test once every eighth week to ensure the treatment response is going, as it should. Other tests to monitor the functioning of the liver and bone density are also performed during different periods of the treatment.

LHRH antagonists are usually not recommended for patients who have irregular heartbeats, liver problems, and osteoporosis as they can exacerbate these conditions, or overweight as this can decrease the effectiveness of the drug absorption.

Examples are degarelix (Firmagon®), Ganirelix (Olganlutran®)

2.6.1.4.2 LHRH / GnRH agonists

Luteinizing hormone-releasing hormone (LHRH) agonists are synthetic analogues of the normal human hormone luteinizing hormone-releasing hormone, which is produced in the human hypothalamus. LHRH stimulates the production of a second hormone known as luteinizing hormone (LH, which under normal circumstances stimulates testosterone production.

All LHRH agonists are small synthetic proteins and are structurally similar to normal human LHRH. However, they are much more powerful than the normal form.

The LHRH agonist has several effects:

1. It stimulates production of LH, which then stimulates production of testosterone. This means that for a couple of weeks the patient's testosterone level will usually rise instead of falling. This increase in the patient's testosterone level can briefly stimulate increased growth of prostate and prostate cancer cells (with associated symptoms, such as increased bone pain, if the patient already has metastases to the bone). This has become known as the "flare response." This response is short-lived in most patients, lasting for perhaps 7 to 10 days.
2. Because the patient now has elevated levels of an LHRH agonist, the body stops producing any new normal LHRH. Consequently, there is no further production of LH or testosterone. The level of hormone then drops by 90 to 95 percent, which is similar to castration levels.
3. Because the testosterone level has dropped to castrate levels, the growth of prostate cells and prostate cancer cells is slowed to very low levels because there is very little testosterone to stimulate growth.

Thus, injection of LHRH agonists can be used to manage the growth and spread of prostate cancer by largely shutting down certain normal hormonal functions in the male. With this treatment, patients regularly see their physician (every 3 months) to monitor the disease and for the medication injections.

Another advantage of LHRH therapy is the elimination of the need for an orchiectomy in those men preferring not to have the surgery. Furthermore, an advantage of LHRH therapy is that the side effects associated with the disease are potentially reversible depending on the length of time that a man has been on treatment. The main disadvantage to LHRH is the costs associated with the treatment.

Examples are goserelin (Zoladex®), leuprorelin (Prostap®) triptorelin (Decapeptyl®), leuprorelin acetate (Eligard®)

2.6.1.4.3 Anti-Androgen Therapy

Anti - androgens work by blocking the testosterone receptors in the prostate cells. Normally, testosterone (also the one produced by the adrenal gland) would bind with these receptors and fuel the growth of prostate cancer cells. With the receptors blocked, testosterone cannot "feed" the prostate. Anti - androgen therapy does not eliminate testosterone and therefore may have fewer or less severe side effects than those associated with surgical and medical castration.

The three most common anti - androgen drugs are:

- Bicalutamide (Casodex)
- Flutamide
- Nilutamide (Nilandron)

These drugs are taken orally as either a tablet or a pill. A single dose usually contains between 50 mg and 150 mg, depending on the patient's needs and doctor's prescription.

The main advantage of anti-androgens is that they do indeed block testosterone from binding to its receptor, as well as any residual testosterone that may not be blocked by LHRH therapy. The main disadvantages include cost and compliance as well as drug-related side effects. Some of these medicines must be taken several times per day and the patient may forget to take all the needed medicine. It is important to take all the prescribed doses of these medicines so that they have their maximal benefit. The anti-androgen Flutamide may cause diarrhoea and Nilutamide may cause a delayed adaptation to darkness, which may affect night time driving.

2.6.2 Metastatic prostate cancer (T4- stage with M1)

If distant metastases (M1) are discovered, then Androgen deprivation treatment (ADT) is initiated. Although as ADT, an LHRH antagonist or an LHRH agonist with or without a Non-steroidal anti-androgen-(NSAA) are recommended as acceptable options, there is not enough clinical evidence to firmly recommend one option over the other as standard therapy (Samson, DJ et al., 2002).

A bisphosphonate therapy should be initiated to avoid/decrease bone loss. Surgery Transurethral Resection of the Prostate (TURP) or radiation therapy can be done to lessen urinary symptoms.

2.6.2.1 Treatment of Bone Complications

Patients with advanced prostate cancer can have cancer cells that have spread to their bones, called bone metastases. Bone metastases commonly cause pain, increase the risk of fractures, and can lead to a life-threatening condition characterized by an increased amount of calcium in the blood called hypercalcemia. Treatments for bone complications may include drug therapy or radiation therapy.

Zoledronic acid (Zometa®): A bisphosphonate drug can effectively prevent loss of bone that occurs from cancer that has spread to the bones thereby reducing the risk of fractures, and decreasing pain. Bisphosphonate drugs work by inhibiting bone resorption, or breakdown. Zoledronic acid may be used to reduce the risk of complications from bone metastases or to treat cancer-related hypercalcemia (Fizazi and al., 2011).

Denosumab (Xgeva™): It targets a protein known as the RANK ligand. This protein regulates the activity of osteoclasts (cells that break down bone). Studies have suggested that Denosumab may be more effective than Zoledronic acid at delaying bone complications in prostate cancer patients with bone metastases. Denosumab is associated with side effects including hypocalcaemia (low levels of calcium in the blood) and osteonecrosis of the jaw (death of bone in the jaw (Fizazi and al, 201; Smith and al., 2011).

Radium Ra 223 dichloride (Xofigo®): It is a targeted radiopharmaceutical agent that binds with minerals in the bone to deliver radiation directly to bone tumours, thereby limiting the damage to the surrounding normal tissues.

2.6.3 Hormone refractory prostate cancer

Patients who experience disease progression despite ADT are treated with secondary hormonal manipulations or chemotherapy.

2.6.3.1 Chemotherapy

Taxanes are the only cytotoxic chemotherapy agents that significantly prolong overall survival in clinical trials in men with castration resistant prostate cancer.

Docetaxel, given at a dosage of 75 mg/m^2 , is administered every three weeks in combination with daily prednisone (5mg twice a day). This combination was found to significantly prolong overall survival and thus used as the standard initial regimen in castration resistant prostate cancer (Basch, 2007). Myelosuppression is a major side effect.

Cabazitaxel is a synthetic taxane derivative developed to have activity in patients who progressed after treatment with docetaxel. According to De Bono JS et al (2010) in their phase III trial, the combination of cabazitaxel and prednisone has shown to significantly increase survival in men whose disease had progressed on docetaxel. As side effect, Cabazitaxel causes significant myelosuppression and requires premedication to minimize the risk of infusion reactions. The contraindications include underlying hepatic dysfunction or compromised bone marrow function.

Mitoxantrone was the first chemotherapy agent approved for use in men with castration resistant prostate cancer. Mitoxantrone was approved based upon improvement in symptoms, and not a prolongation of survival. Its use now is generally limited to patients requiring chemotherapy, who have progressed on or are not candidates for taxane chemotherapy (Dawnson, 2014, UpToDate).

The most common side effects of chemotherapy are:

- Fatigue,
- Nausea and vomiting,
- Diarrhoea,
- Hair loss,
- Taste changes,
- Decrease in blood cell counts that result in an increased risk of infections.

To minimize the side effects, chemotherapy drugs are carefully monitored according to the amount and number of times they are administered.

2.6.3.2 Androgenic biosynthetic pathway inhibitors

Abiraterone Acetate (AA) is a potent, selective, and irreversible Cytochrome (CYP17A1) inhibitor. At high levels, AA also functions as an AR antagonist (Richards et al., 2012). An orally administered small molecule that irreversibly inhibits the products of the CYP17 gene (including both 17, 20-lyase and 17-alpha-hydroxylase). In doing so, Abiraterone blocks the synthesis of androgens in the tumour as well as in the testis and adrenal glands. Patients treated with Abiraterone are at risk for adrenal insufficiency and require concurrent steroid replacement therapy.

In two-phase III trials, Abiraterone plus Prednisone prolongs overall survival compared with prednisone alone in men who had previously been treated with docetaxel (de Bono, 2011). This drug is generally well tolerated, although fluid retention, hypokalaemia, and hypertension may require treatment.

2.6.3.3 Androgen receptor antagonists

Antiandrogens block the effects of circulating androgens with fewer adverse effects (hot flashes, loss of libido, impotence) than are associated with surgical or medical castration. They may be useful in patients whose initial ADT included either medical orchiectomy with a LHLR/ GnRH agonist alone or surgical orchiectomy.

Enzalutamide also called MDV3100 is an orally administered agent that acts at multiple sites in the androgen receptor-signalling pathway, including blocking the binding of androgen to the androgen receptor, inhibition of nuclear translocation of the androgen receptor, and inhibition of the association of the androgen receptor with nuclear DNA.

Enzalutamide has limited activity in men with castration resistant prostate cancer who have previously been treated with both docetaxel and Abiraterone. As an example, in a retrospective case series, approximately 10 percent of such patients had a ≥50 percent decrease in serum PSA during treatment with enzalutamide (Bianchini, 20141). Two different phase III clinical trials were performed to examine MDV3100's effects in CRPC pre- or post-chemotherapy treated

patients (Agarwal et al., 2012; Scher et al., 2012). The trials showed that MDV3100 increased overall survival in post-chemotherapy PCa patients (18.4 months versus 13.6 months).

2.6.3.4 Immunotherapy

Immunotherapy exploits the immune system to delay or halt malignant growth either by targeting tumour-associated antigens (TAAs) or by disrupting molecular pathways that promote tumour growth. The underlying mechanism that makes vaccines so successful is the stimulation of protective immune responses directed against target antigens that are expressed by the infectious agent but not by the host's own cells.

Sipuleucel-T (Trade name Provenge) is a dendritic cell vaccine that is prepared from peripheral blood mononuclear cells obtained by leukapheresis. These cells are exposed ex-vivo to a novel recombinant protein immunogen, which consists of prostatic acid phosphatase (PAP) fused to human granulocyte macrophage colony-stimulating factor. These activated cells are then infused back into the patient approximately three days after the original harvesting.

In randomized trials, Sipuleucel-T prolonged overall survival compared with placebo in men with minimally symptomatic, metastatic prostate cancer (Kantoff, 2010).

Treatment is contraindicated in patients who are on steroids or opioids for cancer-related pain, and should be used with caution in patients with liver metastases.

2.6.3.5 Radiation therapy

Radium-223: It is an alpha particle emitting radiopharmaceutical. It minimizes toxicity to normal bone marrow and to other organs.

In a phase III trial, treatment with radium-223 was well tolerated and increased both overall survival and time to first symptomatic skeletal-related event (external beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic fracture, occurrence of spinal cord compression, or tumour-related orthopaedic surgical intervention) in patients with symptomatic bone metastases and no known visceral metastases (Parker, 2013). Because of its mechanism of action, its use is limited to patients who have bone metastases without other clinically significant sites of disease.

2.7 PROGNOSIS

If given enough time, all patients with metastatic disease become resistant to androgen ablation. The median time to symptomatic progression after a rise in the PSA level of more than 4 ng/mL is approximately 6 to 8 months. Elevated serum levels of markers of bone turnover may be prognostic for poor survival in castration-resistant prostate cancer.

The survival of patients with prostate cancer is related to several factors, including the following:

2.7.1 Patient's age and health

Any benefits of definitive local therapy with curative intent may take years to emerge. Therefore, therapy with curative intent is usually reserved for men with a sufficiently long life expectancy. For example, radical prostatectomy is often reserved for men with an estimated life expectancy of at least 10 years with less to no comorbidities.

2.7.2 Prostate-specific antigen (PSA) level

PSA, an organ-specific marker, is often used as a tumour marker. The higher the level of PSA at baseline, the higher is the risk for metastatic disease or subsequent disease progression. However, it is an imprecise marker of risk.

2.7.3 Extent of tumour

When the cancer is confined to the prostate gland, long-term prognosis is excellent. Patients with locally advanced cancer are not usually curable, but 5-year survival is still very good. If prostate cancer has spread to distant organs, current therapy will not cure it. Median survival is usually 1 to 3 years, and most of these patients will die of prostate cancer.

Prostate cancer metastasizes predominantly to the bone. Other sites for metastases are lungs, liver and lymph nodes. According to one autopsy study, about 80 % of men with advanced prostate cancer had bone metastases. Metastases to the bone can lead to replacement of the bone marrow, spinal cord compression, severe bone pain, cachexia and death. In patients with localized prostate cancer, the 5-year survival rate is almost 100%, while in patients with distant metastases the 5-year survival rate is decreased to 31%.

Despite the steady decline in the incidence of newly diagnosed metastatic prostate cancer and microscopic lymph node metastasis, the risk of extra prostatic disease in patients with clinically localized disease remains high (30-60%). Depending on the prostate-specific antigen (PSA) value, pathologic stage, and histologic grade of the tumour, approximately 50% of patients with clinically localized prostate cancer are estimated to progress despite initial treatment with intent to cure.

3 MATERIALS AND METHODS

3.1 MATERIALS

3.1.1 Subjects

This retrospective study took place at Pauls Stradins Clinical University Hospital (PSKUS) outpatient clinic in the department of Urology. Numerous Patient data were collected and reviewed to find those that meet the research criteria from a period of September 2014 to Mars 2015.

The criteria I looked for in the patients' data was as followed: all living patients with a diagnosis of Prostate adenocarcinoma (ICD-10-CM Diagnosis Code C61), having or have had a hormonal treatment and whose clinical data shows increase in PSA during the treatment were included in this study. The exclusion were death, hormonal treatment with no PSA increase.

3.2 MEDTHODS

3.2.1 Clinical data collections

The initial step was to elaborate a data collection table (see appendix 8.1).

With the help of this data collection table, I was able to collect patients' ID, age, diagnosis according to biopsy, PSA before treatment and during treatment. The presence or absence of metastatic events by bone scintigraphy was also registered.

In addition to the data collection table, I formulate a questionnaire (appendix 8.2) that was going to be used in a phone call survey. Patients meeting the mentioned criteria (see above) were contacted by phone. In order to accomplish this task one Latvian and one Russian translators helped conduct the phone survey. The questionnaire of the survey contained questions concerning the time of diagnosed, the different side effects present (hot flashes, change in bowel habits, erectile dysfunction, tiredness, general pain, back pain, memory loss, anaemia, heart attack). It also contains questions on the overall satisfaction of the patients and missed appointments.

3.2.2 Statistical analysis

All collected data were imported to the software SPSS Statistics (version 22, IBM) and statistically analysed. Descriptive statistics, Chi square test, KruscalK-Wallis test, Pearson and spearsman's correlations were used for that purpose. Results with a $p \leq 0.05$ were considered statistically significant. Tables and Graphs were created with Microsoft Excel and SPSS.

3.2.3 Ethical considerations

The study protocol was approved by The Local Ethics Committee before the study began and was abided by the rules of The Declaration of Helsinki.

4 RESULTS

4.1 DEMOGRAPHY

46 patients were qualified to be in the study. The median age of the patients was 74 years (SD ± 5.5) *(table 1).* Eight patients (17.4%) were ≤ 69 years old 29 patients (63%) were between 70-79 years old and nine patients were ≥80 years old. To make the statistic calculations easier I decided to regroup these patients into two groups, those being ≤74 years old and those being ≥75 years old *(table 2).*

	N	Minimum	Maximum	Mean	Median	Std. Deviation
Patients' age	46	63	88	74.76	74.00	5.506

Table 1- show the mean age, the standard deviation or SD, and the median age of the patients. Note the mean and median age value are not far away from each other

Age_group1	Frequency	Percent	Valid Percent	Cumulative Percent
<74 years	24	52,2	52,2	52,2
>75 years	22	47,8	47,8	

Table 2: Percentage of patients according to the age group.

4.2 REFRACTORY STATUS

The median time between the Prostate specific antigen (PSA) before treatment and its first rise during treatment is 1.5 years (SD ± 2) or 19 months. The minimum range is 4 months and the maximum range is 11 years. This tells us that most of the patients became refractory at around two years after they have started with hormonal treatment (*table 3*).

	N	Minimum	Maximum	Mean	Median	Std. Deviation
Time of PSA increase, years	46	0.50	11.00	2.3717	**1.5**	2.19521
Time of PSA increase, months	46	4.00	136.00	28.5000	19.0	26.68229

Table 3: Refractory time. Note time in months and in years

4.3 PSA FLUCTUATIONS

The median value of PSA before treatment was 17.5 (SD ± 281) with values ranging between 4- 1498 ng/dl. While during treatment the median value was 16 (SD ± 36), with values ranging from 2-161 ng/dl. Using the values of PSA during treatment, I was able to make a graph that shows the PSA fluctuation across time.

In figure 3 and 4 we can definitely see that there is a high fluctuation between 0-2 years, where the PSA during treatment reaches is the highest in the majority of patients. This also reflects over the fact that the majority of patients become refractory at around that time.

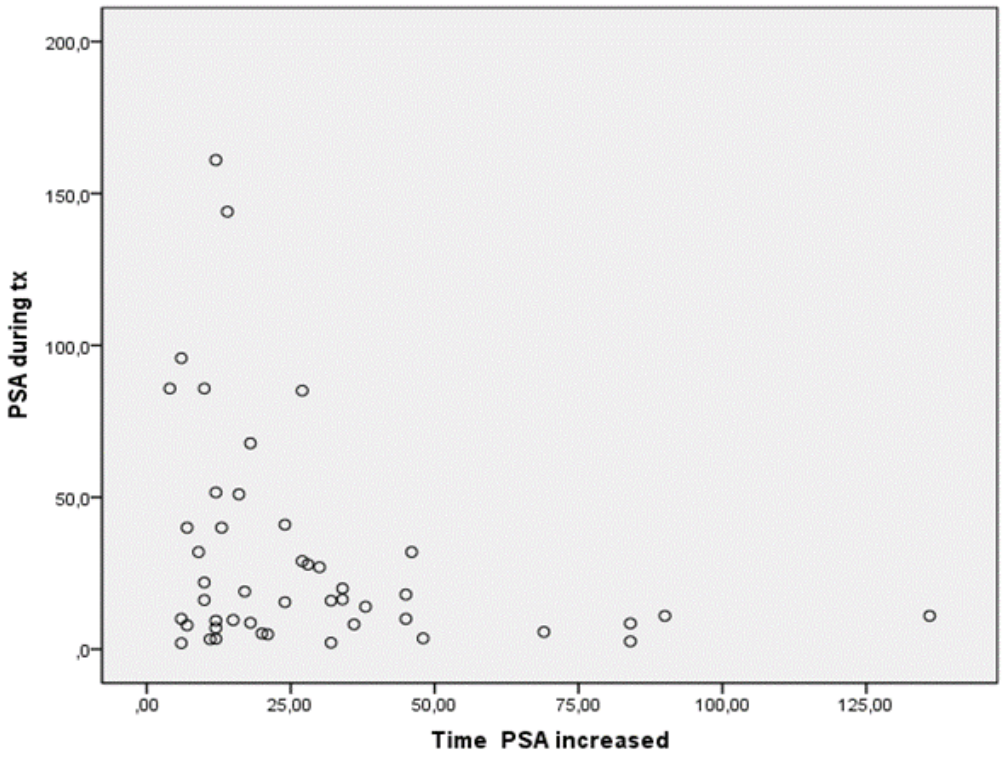

Figure 3: PSA fluctuation during time (months)

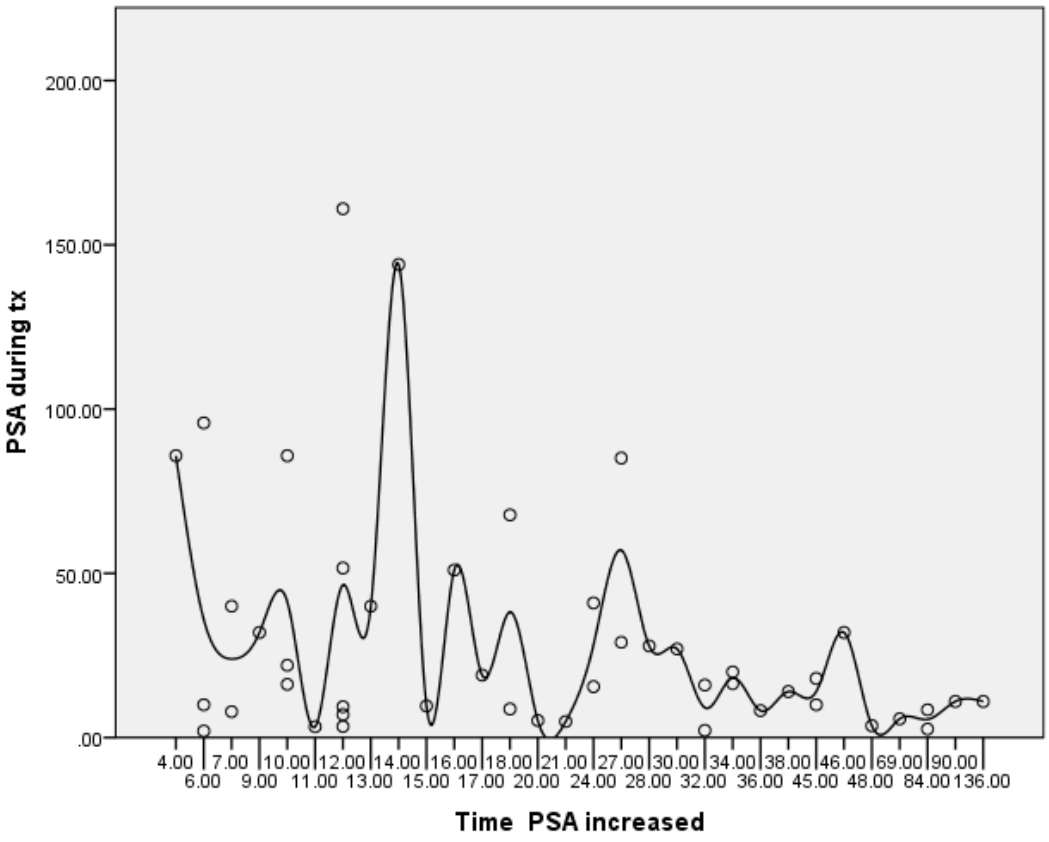

Figure 4: Graph showing PSA fluctuation over time (months)

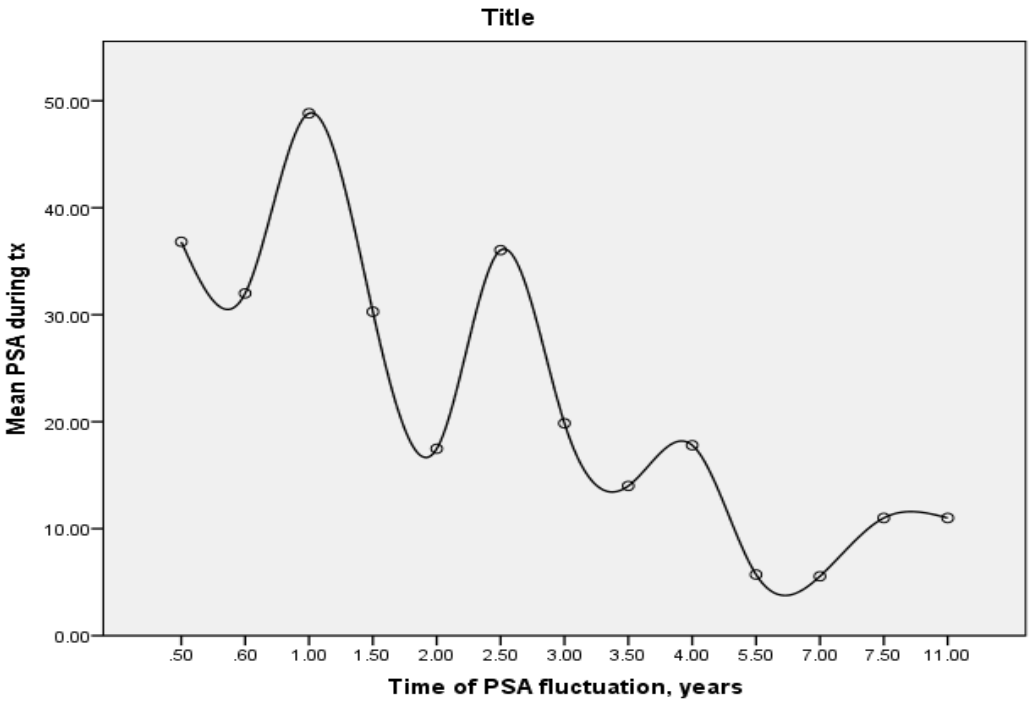

Figure 5: Graph of the PSA fluctuation during treatment.

4.4 SIDE EFFECTS

During treatment, the most common side effects were the presence of hot flashes (67.4%). Urinary retention and weakness were at the same level (58.7%) and back pain (45.7%).

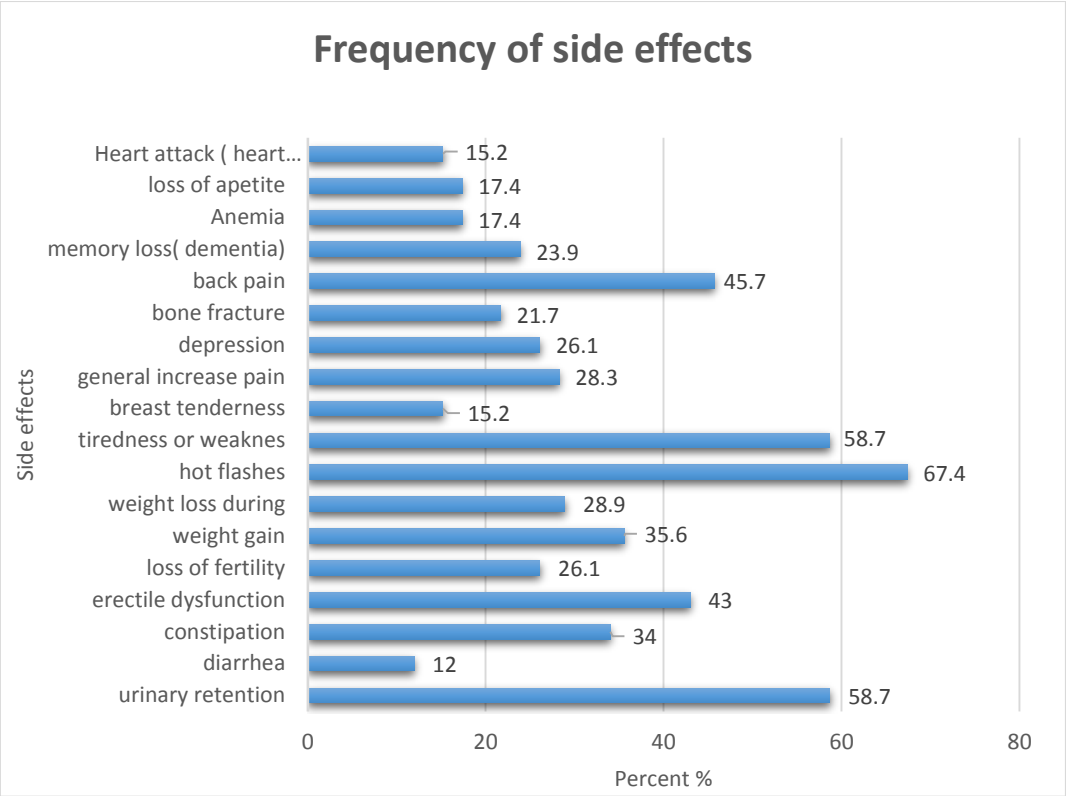

Figure 6: Frequency of side effects

78.3% of patients stated to have not received any treatment for their side effects compared to 21.7% that have received some treatment. (*Figure 7*).

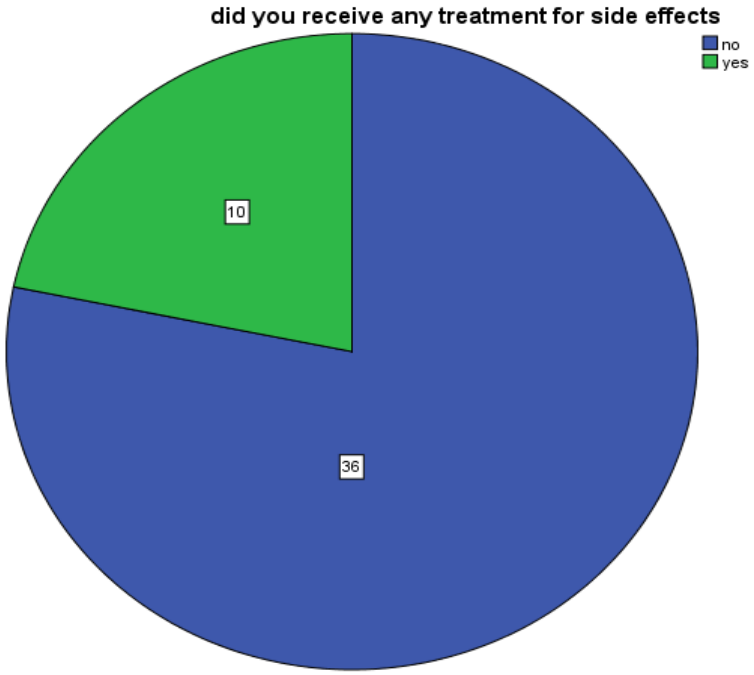

Figure 7: Proportion of patient who received treatment for the side effect and those who did not. Number the pie shows the prevalence.

65% of patients stated that the side effect have not resolved while 35% answers having less or no side effects *(figure 8).*

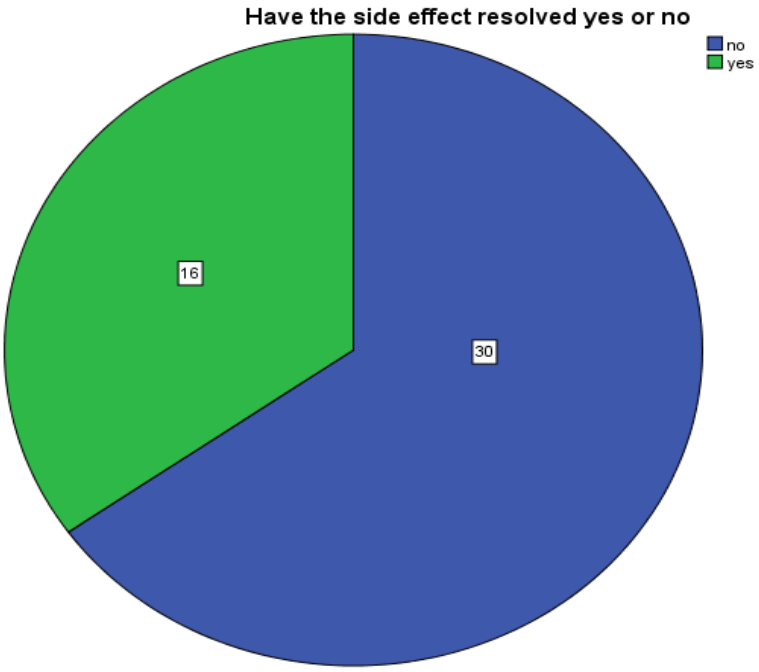

Figure 8: Proportion of patients whose side effects have resolved and those who still have side effects. Numbers in the pie show the prevalence.

In the paired t-test between the patients with resolved side effects and those satisfied with their treatment, we can see a statistical significance supporting the null hypothesis that patients with resolved side effect tend to be more satisfied than the contrary, $p<0.001$ (*table 4*).

Paired t- Test						
	Mean	t	Std. Deviation	95% Confidence Interval of the Difference		P value
The side effect have resolved - satisfied patients with the overall treatment	-7.076	29.894	1.605	7.553	6.599	**0.0001**

Table 4: paired t- test show the p value between patients that have side effect resolved and those that are satisfied with their treatment.

4.5 PATIENTS COMPLIANCE TO TREATMENT

The time that the patients visited the doctor varies according to their treatment progression. 78.3% saw the doctor every third month compared to 17.4 % at 6th month and 4.3 % at 1 year. 24.6 % of patients stated to have missed a doctor's appointment once.

The majority of patients had a satisfaction score of 8/10 (34.78%).

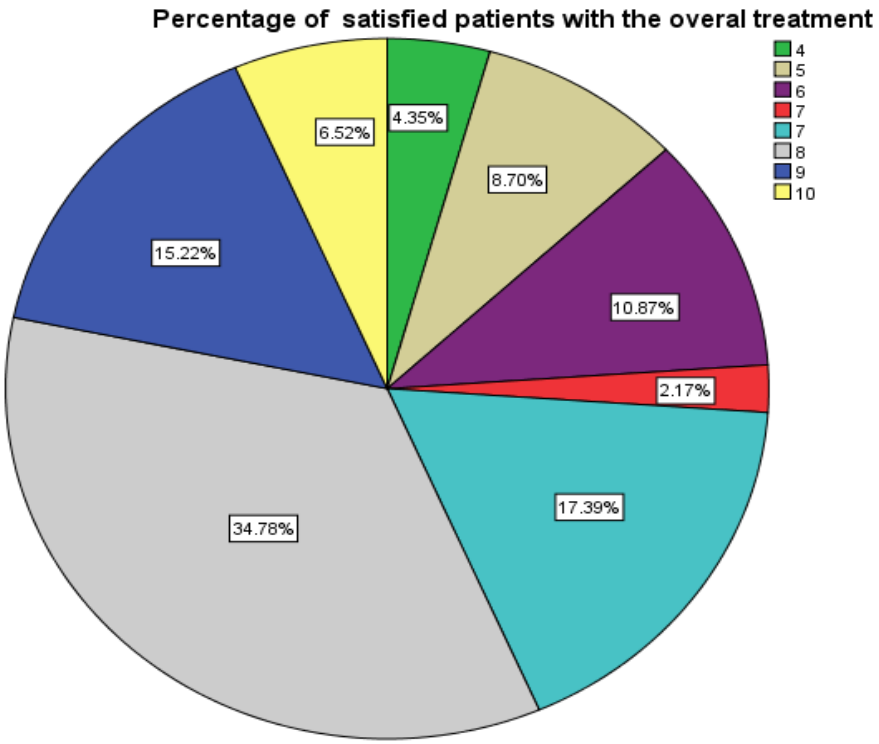

Figure 9: Pie chart showing patients' satisfaction from a scale of zero (not satisfied) to 10 (very satisfied)

With the Spearman's correlation test, we can see that there is a positive correlation between satisfied patients and regular trimestral doctors visit, r= 0.26, p = 0.03.

	Spearman's correlation coefficient	P values (2 –tailed)
Trimestral visit to the doctor and percentage of satisfied patients	0.263	0.03

Table 6: Spearman's correlation test between doctors' appointment attendance and patient satisfaction

Using a null hypothesis stating that the more the patient are satisfied the less they will miss the appointment, we could establish a 2-tailed statistically significant correlation between the two variables, r= -0.47, p= 0.001 (*table 7)*

Spearman's rho		Satisfied patients with the overall treatment	P value (2-tailed)
Missed appointments	Correlation Coefficient	-.457**	0.001

**. Correlation is significant at the 0.01 level (2-tailed).

Table 7: Spearman's correlation between satisfied patients and missed appointment

4.6 PROGNOSTIC FACTORS

4.6.1 Stage of cancer

Based on clinical anamnesis stage II and III were the most common among the patients refractory prostate cancer with respectively 41.3% and 39.1%.

Tumour stage

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Satge2 T1b-T2	19	**41.3**	41.3	41.3
	Stage3 T3 N0M0	18	**39.1**	39.1	80.4
	Stage4 Any T N1M1	9	**19.6**	19.6	100.0
	Total	46	100.0	100.0	

Table 8: frequency of tumours stages

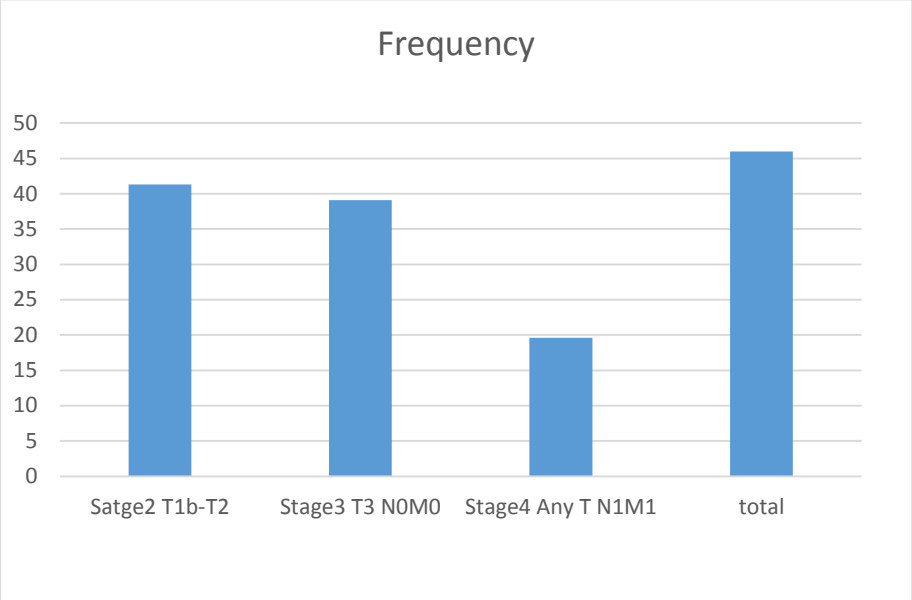

Figure 10: Graph showing frequency of cancer stages

4.6.1.1 Correlation between tumour stages and age group

No statistically significant correlation was found between patients' age groups and tumor stages r = – 0.026, p= 0.4 (*table 9*). There is, however, an equadistribution of cancer stages between the age groups (*figure 11*).

Spearman's rho Correlations			
		Tumour stages	Age_group1
Tumour stages	Correlation Coefficient	1.000	-.026
	Sig. (1-tailed)		0.431
Age_group1 (<74 years, >75 years)	Correlation Coefficient	-.026	1.000
	Sig. (1-tailed)	0.431	

Table 9: Correlation between Tumour stages and age group

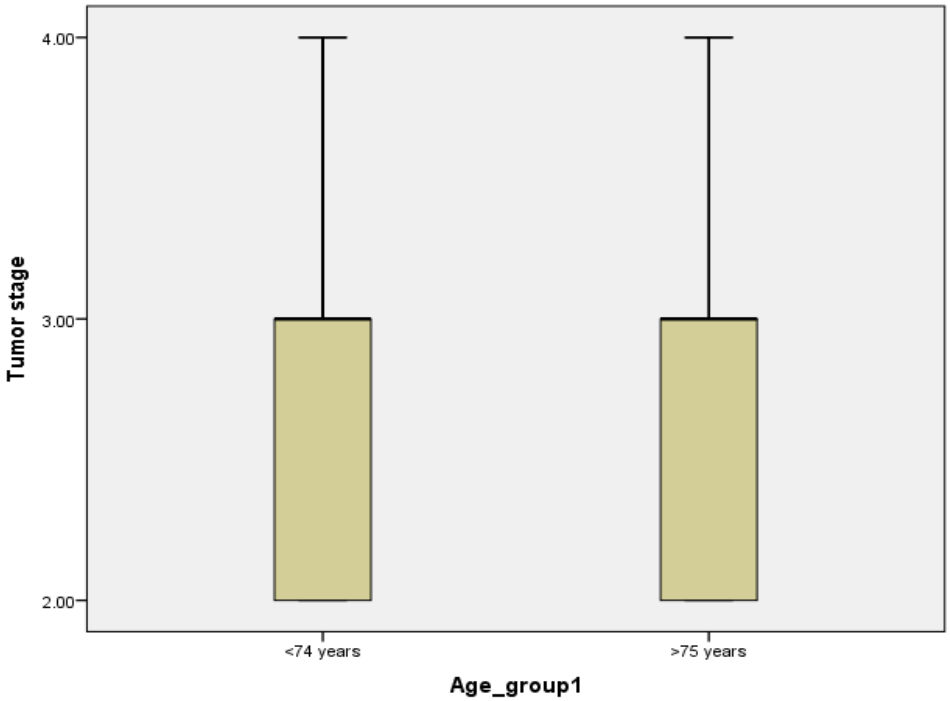

Figure 11: Boxplot showing the correlation between age and tumor stages.

According to Kruskal Wallis Test, there is no significant difference in the distribution of the PSA during treatment across categories of tumor stages, mean rank ranging from 21.2-26.6 and p =0.4 (*table10*).

Kruskal Wallis test

	Tumor stages	N	Mean Rank	Chi square	P value
PSA during tx	Satge2 T1b-T2	19	26.63	1.768	0.4
	Stage3 T3 N0M0	18	21.17		
	Stage4 Any T N1M1	9	21.56		
	Total	46			

Table 10: correlation between PSA during treatment and tumor stages

4.6.2 Gleason score

The mean value of the Gleason score was 5 (SD ± 5.5). The highest Gleason score was attributed to cancer stage IV with values ranging from 7 to 9, while stage 2 had values ranging from 2 to 9 and 2 to 7 for stage 3 cancer.

4.6.1.2.1 Correlation between tumour stages and Gleason score

The correlation between tumour stages and Gleason score shows a statistical significance at stage III and IV, p=0.02 and p=0.04 repetitively (*table 11*).

Tumour stages	Gleason score	P value (2-tailed)
stage2	0.180	0.232
stage3	-0.344*	0.019
stage4	0.300*	0.043

Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed

Table 11: Pearson's correlation between tumour stages and Gleason score

4.6.3 PSA response as a prognostic factor for survival

To evaluate the PSA as a prognostic factor, mean PSA values during treatment were divided into 3 groups, those ≤ 4 ng/ml, between 4-10 ng/ ml and ≥ 10 ng/ml *(table 12, figure 13).* Each value group was then classified according to the treatment response: PSA value ≤ 4 ng/ml had the best treatment response, PSA value between 4-10 ng/ ml had a good response and PSA value and ≥ 10 ng/ml had a poor response or non-response to treatment *(figure 13).* The patients were classified according to their PSA values.

65.2 % of patients had a mean PSA value of ≥ 10 ng/ml, thus having a poor prognosis compared to 23.9 % with PSA between 4-10 ng/ml, having a good prognosis and only 10.9 % with PSA ≤ 4 ng/ml had the best prognosis, $p < 0.01$.

PSA groups

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	≤ 4 ng/ml	5	10.9	**10.9**	10.9
	4-10 ng/ml	11	23.9	**23.9**	34.8
	≥ 10 ng/ml	30	65.2	**65.2**	100.0
	Total	46	100.0	100.0	

Table 12: Frequency of different PSA values group

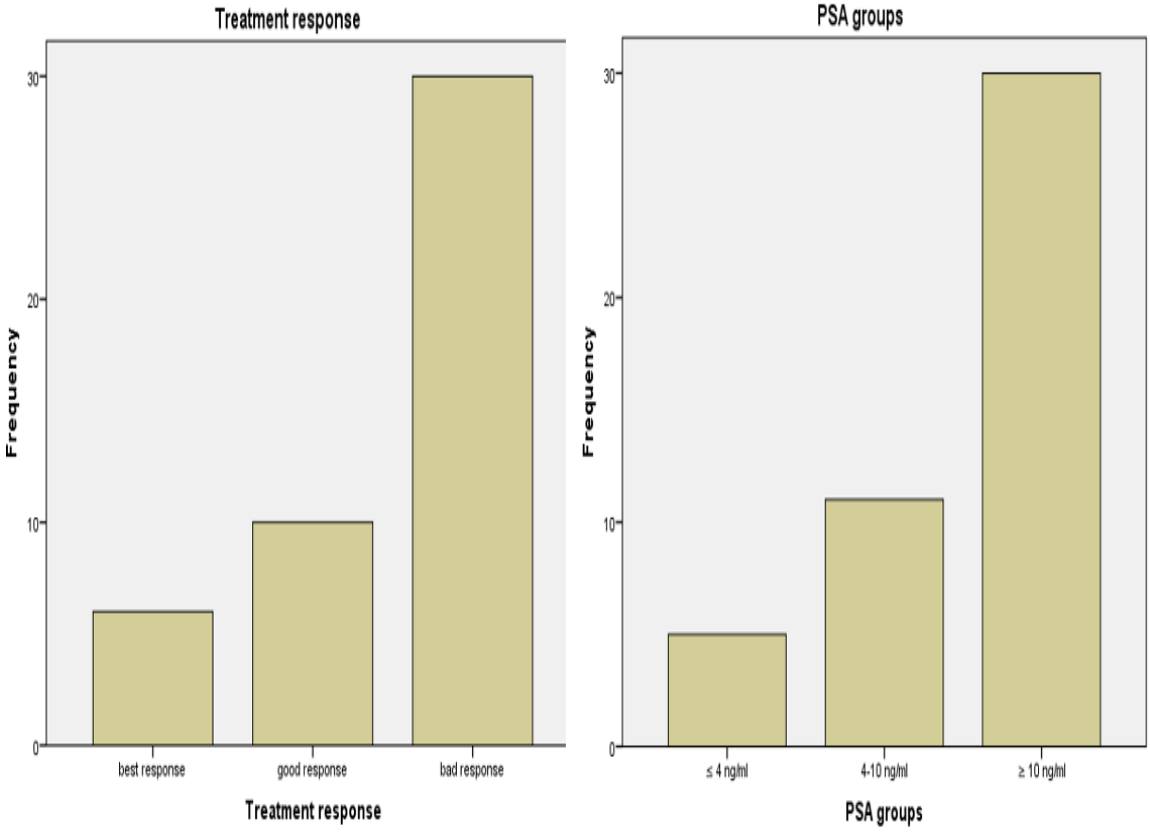

Figure 13: Frequency of PSA values group (right) corresponding to treatment response (left)

5 DISCUSSION

The age distribution in the study was between 63-88 years with a mean age of 74.7 years (SD ± 5.5). This is slightly higher than with the overall mean age of patients with prostate carcinoma mentioned in other research (70.1 years, Plonis, J. et al, 2014). A study done in the UK (Birtle, Alison J.et al, 2003) mentioned a median age of 67 years. This difference can be assumed to occur due to different factors such as increase life expectancy in the overall population, the occurrence of HRPC in the cancer population.

The median time of refractory is found to be 1.5 years or 19 months. This corresponds with other studies (Hotte, S.J. et al, 2010, Sharifi N et al., 2005). The PSA fluctuation was not homogenous considering that the patient groups were also non-homogenous in regards to the treatment stages, the length of their treatment, the length of the cancer life and their cancer stages.

The percentage of patients that have received treatment for the side effect is far less than that of those who have not and such is for those whose side effects have not resolved compared to those whose theirs have resolved. These results can show the lack of consistency in the chain of treatment. As HRPCa patients need a multidisciplinary approach, any lack in the appropriate palliative care will be reflected upon the overall treatment response and patient satisfaction. This can be seen in the correlation between patient who have received treatment and those with resolved side effects($r=0.4$). A linear proportional increase in both variables is indicated by the positive spearman's correlation and a statistical significance, $p = 0.004$, logically meaning that patients who receive treatment for their side effects, will have them resolved and so be more satisfied.

The result also portrays that the distribution between advanced cancer stages is the same in all the age groups. Other research (Bianchi, M. EAU congress press release, 2015) has stated that patients under 60 that have been firstly treated with radical prostatectomy prior to hormonal treatment should be closely monitored, as the majority will die of a cancer related death within the first 10 year of their cancer lives. After 10 years, the distribution tends to be equal in younger and older patients.

Although the correlation ($r = -0.317$) between satisfied patients and regular doctors visit at every 6 months shows that the variable are not increasing in proportionate level, it is still statistically significant at $p \leq 0.05$($p = 0.03$). The interpretation is that the more the patients attend their

doctor's appointments the more they are satisfied and vice versa. This means that if the number of doctor's appointments decrease, then there will be less satisfied patients. This is very much significant to the management of the patients' disease courses. On the other hand, the correlation between patients who are satisfied with their treatment versus those who missed an appointment shows a negative correlation value and a statistical significance at $p = 0.001$, meaning that the more the patients are satisfied with their treatment the less they tend to miss any doctor's appointment.

Concerning the prognostic factor, we can clearly see that there is a strong correlation and statistical significance ($p < 0.01$) between the Gleason score and the tumour stages. The higher the Gleason score, the advance is the tumour stage. The worst prognostic values are found in stage 3 and 4. The same can be said for the PSA value: the greater the PSA value (≥ 10 ng/ml), the lesser the treatment response is obtained and thus constituting a poor prognosis for the patient.

6 CONCLUSION

1. The median time by which the patients became refractory was found to be 1.5 years or 19 months. The minimum range is 4 months and the maximum range is 11 years

2. The PSA during treatment of refractory has a median value of 16 ng/dl, with values ranging from 2-161 ng/dl. Level curve shows a non-homogeneous distribution along the time of refraction.

3. The most common side effect experienced by the patients was the presence of hot flashes followed by urinary retention and weakness. Back pain was at the third place. More patients stated to have not received any treatments for the side effects compared to those who received treatment.

4. The compliance of the patients was found to be very positive as many patients attend their doctor's appointment regularly. The more the patients were satisfied with the overall treatment, the less likely they were to miss any appointment. The time that the patients visited the doctor varied according to their treatment progression.

Concerning the different prognostic factors, the most common stages in our patient pool were cancer stage II and III. 19.6% of patients had metastatic processes. There were no statistically significant correlation between the age group and the tumour stages since the tumour stages were equally distributed between the age groups. The highest Gleason score was attributed to stage IV with values ranging from 7-9. The correlation between tumour stages and Gleason score shows a statistical significance at stage III and IV. Patients with PSA value ≤ 4 ng/ml had the best response to treatment, thus the best prognosis compared to patients with PSA value $\geq$ 10 ng/ml who had a poor or no response to treatment, thus having the worst prognosis.

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8 APPENDICES

8.1. DATA COLLECTION TABLE

Patient's ID	*Age*	*Contact Information*	*Cancer stage*	*Gleason score*	*PSA before HT*	*PSA during HT*	*Metastasis*
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8.2. PACIENTU TELEFONISKĀS ANKETĒŠANAS JAUTĀJUMI

1) Kad jums tika diagnosticēts prostates vēzis?

2) Kāda ir jūsu ārstēšanās pieredze skalā no nulls (ka sir kā ļoti slikta) līdz atzīmei desmit (ka sir kā ļoti laba)?

3) Jūsu ārstēšanās laikā vai jūs pieredzējāt kādu no sekojošām pazīmēm: (jā vai nē):

A) Urīna aizture

- Zarnu disfunkcija:

B) Caureja

C) Aizcietējums

D) Erakcijas disfunkcija

E) Auglības zaudēšana

F) Svara pieaugums, cik liels?

G) Svara zudums, cik liels?

H) Karstuma viļņi

I) Nogurums

J) Vājums

K) Krūšu jūtīgums

L) Sāpju pieaugums

M) Depresija

N) Kaulu lūzumi

O) Ostiporoze, , muguras sāpes

P) Atmiņas zudums. demence

Q) Anēmija

R) Apetītes zudums

S) Sirdslēkme (sirds problēmas)

4) Ja uz kādiem no šiem jautājumiem atbilde ir jā, tad kāda bija jūsu ārstēšanās pieredze (vai attieksme prêt jums mainījās, vai jūs saņēmāt papildus aprūpi šo blakusparādību dēļ?)

5) Vai blakusparādības ir novērstas? Ja jā, tad cik ilgu laiku to novēršana aizņēma?

6) Kā jūs tagad jūtaties skalā no 0 (ļoti slikti) līdz 10 (ļoti labi)

7) Vai esat apmierināti ar ārstēšanas procesu tik tālu? No 0 (neapmierināts) līdz 10 (ļoti apmierināts)

8) Cik bieži jūs satiekat savu aprūpējošo ārstu? Ik mēnesi, katrus trīs mēnešus, katrus sešus mēnešus, reizi gadā.

9) Vai esat kādu tikšanos palaidis garām? Ja jā, vai plānojat vizīti pie ārsta tuvākajā laikā?