

A RETROSPECTIVE STUDY COMPARING ABIRATERONE ACETATE AND ENZALUTAMIDE IN THE TREATMENT OF PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER IN SPLIT

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**UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE**

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1. INTRODUCTION

1.1 Anatomy and histopathology

The prostate gland, a triangular shaped organ weighing around 20g to 30g is located anterior to the rectum, inferior to the urinary bladder and surrounds the bladder neck and proximal urethra. It can be categorised into five lobes, the anterior lobe, median lobe, two lateral lobes and the posterior lobe. In a healthy young male, the physiologically normal dimensions are approximately 4cm in width, 3cm in height and 2cm in length (1).

The prostate gland is divided into three main zones each with different embryological origins. These are known as the peripheral, central and transition zones. In a young adult these areas account for 70%, 25% and 5% of the volume of the prostate gland respectively. The vast majority of prostate carcinomas arise in the peripheral zone and 60-70% are found in this area (2). Regarding histology, over 90% of prostate carcinomas are adenocarcinomas. The remaining 5% are heterogeneous which includes cells of stromal, epithelial, or ectopic origin (2).

1.2 Epidemiology and risk factors

In Western populations, prostate cancer has become the most common male cancer and the third most common cause of cancer death in Europe. In Croatia, prostate cancer is the third most common male cancer after lung and colorectal cancer (3).

The geographical distribution of prostate cancer incidence differs extensively among different populations and ethnicities worldwide. The most commonly affected regions include Australia, New Zealand, North America and Northern and Western Europe. Incidence rates are also relatively high in less developed regions such as the Caribbean, South Africa and Southern America. On the contrary, the lowest rates have been reported in Central and Eastern European countries and Asia (4).

Prostate specific antigen (PSA) is a screening measure that is more effective at detecting incidence than it is at detecting mortality. Access to screening varies in different regions and as a result, leads to a disparity in incidence rates in the world. On the other hand, mortality remains stable regardless of location (4).

The increased incidence of prostate cancer can be attributed to various reasons. Firstly, there is a longer average life expectancy compared to the past. More people live longer than 70 years and are therefore more likely to reach an older age in which prostate cancer incidence is higher. Secondly, an increased diagnostic rate especially in the use of PSA for screening asymptomatic, otherwise healthy individuals has led to a significant increase in the age-adjusted incidence rates of the disease. Consequently, prostate cancers that are small and would have previously gone undetected are found and recorded (5). The discrepancy among regions in the world may reflect access to preventive and diagnostic tools. Further to this, the differences may be attributed to other aspects such as genetic, environmental factors, diet and lifestyle (4).

There are three well-established risk factors for prostate cancer: old age, a positive family history and ethnicity. Firstly, the average age for a diagnosis of prostate cancer is 67 years and the median age for death is 81 years (6). Out of all cancers, the incidence of prostate cancer increases the most when it comes to age. In fact, it is almost universal at postmortem in men aged over 80 years (5). Moreover, patients who have a first-degree relative with a diagnosis of prostate cancer have double the risk of developing prostate cancer compared to those who do not have a diagnosed first-degree relative (6). When it comes to race, the mortality rate among African-American men is almost twice that of Caucasian men. Furthermore, there is a higher mortality rate in less developed countries as opposed to developed countries (4).

Further risk factors include the total dietary fat intake; animal fat and red meat are associated with an increased risk. Consumption of fish, conversely, has been shown to be protective. Additionally, lycopene, selenium, vitamin E and omega-3 fatty acids correlate with a lower risk, whereas vitamin D and calcium increase the risk (2).

1.3 Screening

Prostate cancer screening is a set of diagnostic tests which is performed at regular intervals aimed primarily at apparently healthy males from the general population. This allows for the detection of cancer in an early pre-clinical phase. As a result, screening has proved beneficial as early management can be initiated which can reduce prostate cancer mortality as well as maintain quality of life (7).

Current EU guidelines recommend that screening should begin early for men who are at increased risk of prostate cancer. Men who fall under this category are those who are over 50 years, over 45 years of age with a family history of prostate cancer, African-Americans, men with a PSA level of > 1 ng/mL at 40 years of age and men with a PSA level of > 2 ng/mL at 60 years of age (7).

Prostate cancer is usually suspected on the basis of PSA measurement and digital rectal exam (DRE). In previous years, DRE was the principle method of prostate cancer screening. However, there is a variability of detection among different examiners and the majority of cancers detected with this method are already at an advanced stage. Furthermore, the positive predictive value is only 11%–26% and so when used alone DRE is insufficient for screening (8). This method has now been surpassed by PSA measurement which came into practice in 1980. Although there is no evidence to suggest that testing reduces the risk of death from prostate cancer it does however allow for patients to be categorised into those who will develop clinically significant disease from those who will not (5). For a total PSA value to be considered normal it should be below 4 ng/ml. A PSA between 4 and 10 ng/ml has a positive predictive value of around 20-30%. When the value exceeds 10 ng/ml the positive predictive value increases to 71.4% (2). An elevated PSA level will warrant further evaluation.

There are some limitations to using PSA measurements and these should be taken into consideration. The main issue is that PSA is prostate specific but not prostate cancer specific. False positive results can be obtained because other benign prostate conditions can also elevate PSA levels. Examples include BPH, prostatitis, urethral instrumentation and perineal insults (2). These should be kept in mind when a patient has an elevated PSA level.

Free PSA can be measured in order to distinguish prostate cancer from benign disease in patients with total PSA values between 4 and 10 ng/ml. Patients with prostate cancer typically produce more complexed PSA in which PSA is bound to proteins. In contrast, benign prostate cells produce more free PSA. The ratio of free to total PSA can facilitate the decision of whether a biopsy is appropriate for the patient (9).

Patients who have an elevated PSA level, abnormal DRE or a combination of the two should be considered for a transrectal ultrasound (TRUS) guided biopsy. Twelve core biopsies are obtained from the prostate gland at the base, mid-gland and apex. The definitive diagnosis can subsequently be confirmed by histopathological analysis (10).

1.4 Symptoms and presentation of prostate cancer

Many asymptomatic prostate cancers have been identified as a result of screening. When prostate cancer does become symptomatic, it may cause a patient to experience any of the following symptoms: impotence, urinary retention, urinary frequency, urinary hesitancy, nocturia and hematuria. A number of these symptoms do however overlap with benign prostate conditions which are more likely to be the cause. For example, patients with benign prostate hypertrophy often complain of urinary frequency, urgency, and hesitancy (11).

Symptoms of prostate cancer vary depending on how far the disease has progressed and whether the spread is lymphatic, hematogenous or contiguous (12). Prostate cancer can spread locally to the seminal vesicles, ureters, bladder base and external urethral sphincter which typically leads to the symptoms of prostatism. Lymphatic involvement commonly includes the iliac chain in the early stages and can progress to the para-aortic lymph nodes in more advanced disease. Hematogenous involvement is responsible for metastasis to the bones, liver, lung and adrenal glands (8).

Advanced prostate cancer symptoms include weight loss, anemia, ostealgia possibly with pathologic fracture, neurologic deficits due to spinal cord compression, lower extremity pain and edema due to obstruction of venous and lymphatic vessels by nodal metastasis. Some of the aforementioned symptoms can be explained by the strong predilection of prostate cancer to metastasise to the skeletal system (12). As a matter of fact, more than 80% of those who die of prostate cancer have evidence of this (8). Uremic symptoms can also result if there is obstruction of the ureter due to local prostate growth or retroperitoneal adenopathy secondary to nodal metastasis (12).

1.5 Gleason score

The Gleason score, obtained following biopsy is a grading system for prostate adenocarcinoma based on five histological growth patterns or grades. Many prostate adenocarcinomas demonstrate two or more Gleason patterns. The primary and secondary Gleason patterns are added together to produce the Gleason score (Table 1). They are categorised according to the degree of glandular differentiation (Table 2). The first grade is the most differentiated histology type and therefore represents the most favourable prognosis. On the other hand, the fifth grade correlates to the least differentiated type and thus indicates a poor prognosis (13).

Table 1. Gleason score grading system. This table was taken from Chen N *et al.*

Grade	Gleason score
1	Gleason 6 (or less)
2	Gleason 3+4=7
3	Gleason 4+3=7
4	Gleason 8
5	Gleason 9-10

Table 2. Gleason pattern. This table was taken from Mazhar D *et al.*

Grade	Gleason score
1	Well differentiated carcinoma with uniform gland pattern
2	Well differentiated with glands varying in size and shape
3	Moderately differentiated carcinoma
4	Poorly differentiated carcinoma with fused glands
5	Very poorly differentiated carcinoma with no or minimal gland formation

1.6 Staging

Following biopsy, prostate cancer can be staged according to the TNM classification. This acronymic classification system represents the size of the tumor (T), the lymph node involvement (N) and the presence of metastases (M) (Figure 1). In addition to evaluating the risk of prostate cancer spreading beyond the prostate gland, the TNM score can establish whether local therapy, such as surgery or radiation is appropriate (14).

Prostate Cancer TNM Staging		
T (Tumor)	TX	Tumor cannot be assessed
	T0	No evidence of primary tumor
	T1	Tumor not clinically apparent
	T1a	Tumor found in resected specimen (<5%)
	T1b	Tumor found in resected specimen (>5%)
	T1c	Tumor found at biopsy for elevated PSA
	T2	Tumor confined to prostate
	T2a	Tumor involves ≤50% of 1 lobe of prostate
	T2b	Tumor involves >50% of 1 lobe of prostate but not 2 lobes
	T2c	Tumor involves both lobes of prostate
	T3	Tumor is palpable; extends beyond capsule
	T3a	Tumor extends beyond capsule but not to seminal vesicles
	T3b	Tumor invades seminal vesicles
	T4	Tumor is fixed or invades adjacent anatomy (other than seminal vesicles)
N (Node)	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis to regional lymph nodes
M (Metastasis)	MX	Presence of distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis
	M1a	Metastasis to nonregional lymph nodes
	M1b	Metastasis to bone
M1c	Metastasis to other distant sites	

Figure 1. TNM staging score for prostate cancer. This picture was taken from <http://reference.medscape.com/slideshow/prostate-cancer-6004678#18>.

Prostate cancer is categorised from stage I (the least advanced) to stage IV (the most advanced) using information obtained from the TNM stage, Gleason score and PSA (Figure 2). The treatment and prognosis can then be determined by the stage allocated to that particular patient (14).

Stage	T	N	M	PSA*, ng/mL	Gleason Score				
I	T1a-c	N0	M0	PSA <10	Gleason ≤6				
	T2a								
	T1-2a								
IIA	T1a-c			N0	M0	PSA <20	Gleason 7		
	T2a								
	T2b								
IIB	T2c					N0	M0	PSA <20	Gleason ≤7
	T1-2								
III	T3a-b					N0	M0	Any PSA	Any Gleason
	T4								
IV	Any T	N1	M1	Any PSA	Any Gleason				
		Any N							

*If the PSA or Gleason is not available, determine the stage by T stage and/or either PSA or Gleason, as available.

Figure 2. Staging of prostate cancer. This picture was taken from <http://reference.medscape.com/slideshow/prostate-cancer-6004678#18>.

1.7 Risk stratification

Current trends of prostate cancer management show overtreatment of low-grade disease and undertreatment of high-grade disease. With the intention of reducing this pattern, over 100 risk formulae, lookup tables, nomograms, and other tools have been developed to target this and stratify risk accordingly (2).

Risk stratification is done in order to assess the risk of recurrences following local treatment of prostate cancer which subsequently allows the patient to make a more informed decision about their treatment plan with regards to disease-free survival. At present, localised prostate cancer is risk stratified according to PSA level at diagnosis, Gleason histological grade and T score from the TNM classification (15). This model is based on the D'amico classification which came about in 1998 and allocates each patient into one of three risk groups: low, intermediate and high (16) (Table 3).

Table 3. D'amico risk stratification for clinically localised prostate cancer. This table was taken from <http://www.cancernetwork.com/cancer-management/prostate-cancer/page/0/1>.

Risk	Criteria
Low risk	Diagnostic PSA <10.0 ng/ml <i>and</i> highest biopsy Gleason score ≤ 6 <i>and</i> clinical stage T1c or T2a
Intermediate risk	Diagnostic PSA ≥ 10 but < 20 ng/ml <i>or</i> highest biopsy Gleason score = 7 <i>or</i> clinical stage T2b
High risk	Diagnostic PSA ≥ 20 ng/ml <i>or</i> highest biopsy Gleason score ≥ 8 <i>or</i> clinical stage T2c/T3

Another method of risk stratification is the Cancer of the Prostate Risk Assessment (CAPRA) score. It was developed in 2005 by Cooperberg *et al* and is used to stratify prostate cancer risk preoperatively. Risk is indicated on a scale of 1-10. Points are allocated according to: PSA at the time of diagnosis, Gleason score, clinical stage, the percentage of positive biopsy cores and age. The CAPRA score is now used to predict the risk of bone metastasis and prostate cancer-specific mortality. Each increase in CAPRA score has been linked to an increased risk of prostate cancer specific morbidity or mortality (16).

The National Comprehensive Cancer Network (NCCN) has further improved risk stratification by classifying men into five risk groups as opposed to the original three. In these guidelines, the intermediate group has been split into low-intermediate and high-intermediate groups (16). Additionally, a very low-risk group has been included for patients who have a very low risk of dying from prostate cancer in the next 10 to 20 years. This allows patients to avoid aggressive treatment if they are more suitable for an active surveillance approach (15).

In order to achieve more accurate risk stratification in the future, further information is being added to stratification methods such as MRI and genomic profiling (16).

1.8 Treatment of local Prostate cancer

1.8.1 Watchful waiting and active surveillance

Watchful waiting and active surveillance are both types of expectant management. They involve an initial surveillance which is followed by treatment only in the case of symptomatic disease progression. These conservative management strategies are used with the intention of avoiding over treatment and in doing so preserve quality of life (7).

The principle difference between the two is that treatment in watchful waiting is palliative and in active surveillance it is curative. Therefore, treatment in watchful waiting aims to control disease whereas active surveillance is reserved for patients who are more likely to be cured should treatment be started (17). Moreover, active surveillance involves more frequent investigations than watchful waiting including prostate biopsies and MRIs (7).

Generally, patients who are allocated to watchful waiting are older, have comorbidities and have a low stage of disease. This method is suitable for patients who have a life expectancy of less than 10 years or have another more serious illness that is more life-threatening than their prostate cancer. Moreover, patients with comorbidities are less likely to tolerate treatments such as radiotherapy or surgery (7).

Active surveillance is suitable for patients with a low risk of cancer progression. This subset of patients include those with localised cancer, a life expectancy of more than 10 years and are more likely to tolerate treatment (7).

1.8.2 Radical prostatectomy

Radical prostatectomy involves the removal of the entire prostate gland, adjacent bladder neck, seminal vesicles, vas deferens and the surrounding fascia in the anticipation that the prostate cancer can be completely eradicated (5). Radical prostatectomy is currently considered to be the first line of treatment when it comes to the removal of localised cancer. This is a surgery that is indicated for men who have a life expectancy exceeding 10 years and prostate cancer that is localised to the prostate gland i.e. stages T1-T2. As a sole treatment, it has cured the majority of patients with organ-confined disease or with well-differentiated tumors (18).

Prostatectomy can also be combined with radiotherapy so as to gain a better control over the cancer. Postoperative radiotherapy may be suitable if the area surrounding the excision margins or pelvic lymph nodes are involved (5). Following prostatectomy serial PSA levels are taken in order to assess whether there is any progression of disease (19). PSA should be undetectable and if present suggests that there is residual disease. This is a further indication that postoperative radiotherapy would be beneficial (5).

As with most surgeries, there are a number of side effects and complications to consider following radical prostatectomy. Side effects include short-term constipation, urinary incontinence, erectile dysfunction, infertility, possible blood loss due to the surgery, in rare cases there may be injury to the rectum and there is also a very low chance of post-operative mortality (19).

In the interest of minimising erectile dysfunction, nerve-sparing techniques can be used during surgery to preserve the neurovascular bundle. However, this is not always recommended if prostate cancer is more advanced and cancerous cells may have invaded the surrounding neural structures (19).

1.8.3 Prostate cancer radiotherapy

External beam radiotherapy uses high energy X-rays as a source of ionising radiation from outside the body to target and destroy cancerous prostate cells and discontinue or slow their growth (20). Types of external beam radiotherapy include 3D conformal radiotherapy (3D-CRT) and intensity-modulated radiation therapy (IMRT).

Radiotherapy may be used as a curative or as a palliative treatment. Radiotherapy as a curative therapy is suitable for men who have localised prostate cancer and for those with locally advanced prostate cancer. Patients who have advanced or metastatic cancer may be offered radiotherapy as a palliative measure to help control symptoms such as ostealgia (20).

There are various methods in which radiotherapy is applied. These include radiotherapy as a primary, neoadjuvant, adjuvant and salvage treatment (5). Further discussion of the latter two methods can be found in a subsequent section.

Both 3D-CRT and IMRT allow for treatment planning so that a focused dose of radiation can be targeted at cancer cells. Side effects are reduced because a high dose can conform to the desired target volume whilst sparing the surrounding healthy tissues. 3D-CRT uses CT to create a 3D image reconstruction of the prostate gland. IMRT, on the other hand, allows for modulation of the radiation beam intensity and so higher doses of radiation can be applied compared to 3D-CRT. IMRT may be added to conformal therapy to further intensify the radiation of cancerous tissues (21).

There are various side effects linked with radiotherapy of the prostate gland. These may be short or long-term side effects. Patient risk factors leading to a higher likelihood of side effects are in those who are older, have diabetes melitus, inflammatory bowel disorders, previous abdominal surgery or hemorrhoids (22).

In the short-term, radiotherapy can cause radiation cystitis leading to symptoms such as dysuria, pollakiuria, urinary retention, hematuria and urinary incontinence (20,22). Moreover, radiotherapy can cause gastrointestinal problems including an increased urge to defecate, the discharge of rectal mucus and hematochezia (22). Further short-term side effects include: fatigue, anejaculation, skin irritation and hair loss around the site of radiation (20). Following the cessation of radiotherapy these acute side effects tend to resolve quickly (22).

Genitourinary symptoms, gastrointestinal symptoms and erectile dysfunction, as mentioned previously, may also become long-term side effects. Erectile dysfunction may be successfully treated with phosphodiesterase-5 inhibitors (22). Further long-term side effects include ostealgia and osteoporosis as radiotherapy may damage osteocytes and the blood supply of the surrounding bones. Additionally, semen quality can be affected so patients may decide to collect and store their semen for future use and should consider appropriate contraception (20). Due to the damage caused by radiotherapy, there is a small chance of secondary malignancy formation which can occur after around 10-15 years (22).

1.8.4 Brachytherapy

Patients may also receive brachytherapy alongside external beam radiotherapy. Brachytherapy is another sort of radiotherapy in which radioactive material is placed directly into the prostate gland. There are two different types of brachytherapy based on the rate of radiation. These are either low dose rate (LDR) or high dose rate (HDR) brachytherapy. In LDR brachytherapy radioactive ‘seeds’ are placed into the prostate gland permanently and emit radiation to the prostate and surrounding tissues in order to destroy cancer cells. The radioactive ‘seeds’ are placed via TRUS guidance and contain either iodine-125 or palladium-103 (2). LDR is suitable for patients who have localised prostate cancer. HDR brachytherapy also involves the placement of radioactive material to target cancerous cells, however, unlike LDR, it is temporary and is used over a shorter time period. HDR brachytherapy is more suited to patients with locally advanced prostate cancer and is often used in conjunction with external beam radiotherapy or hormone therapy (23).

1.8.5 Hormone therapy

Prostate cancer is dependent on androgens for its maintenance and progression. Consequently, hormone therapy is effective because it reduces the amount of androgens in the body and thus decreases the growth of the tumor (24).

Hormone therapy is known as androgen deprivation therapy (ADT). ADT directly antagonises androgen receptors at the level of the prostate gland or regulates the release of androgens from the hypothalamic-pituitary axis (GnRH agonists) (5). Flutamide and bicalutamide are examples of androgen receptor antagonists. These can be used alone or in combination with surgical castration to block the effect of androgens. GnRH agonists, on the other hand, include Leuprolide and Goserelin (24).

There are numerous indications for ADT. It may be used as a primary treatment to palliate symptoms in patients who are unsuitable for definitive treatment with surgery or radiation or in those who have relapsed following primary treatment. ADT can also be used in the neoadjuvant setting prior to definitive radiotherapy to shrink the size of the tumor and allow for better symptom control in patients with locally advanced tumors. ADT used as an adjuvant therapy following definitive radiotherapy or surgery has been shown to provide an improvement in survival (5).

The androgen biosynthesis pathway elucidates the mechanism of GnRH agonists. The pathway begins at the level of the hypothalamus which secretes gonadotropin-releasing hormone (GnRH) in a pulsatile manner. This in turn stimulates the adenohypophysis to release the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (25). LH is responsible for the production of testosterone via the Leydig cell receptors which are found in the testes. Approximately 90% of testosterone is synthesised in the testes and the remaining testosterone is synthesised by the adrenal glands from its precursor cholesterol. Testosterone is then converted into its active metabolites; dihydrotestosterone (DHT) and estradiol (24). The continuous stimulation of the GnRH receptors leads to their eventual desensitisation or downregulation which results in suppressed gonadotropin release and a consequent drop of testosterone levels to castrate levels (25).

Upon initiation of treatment with GnRH agonists, there is an exacerbation of clinical symptoms due to the initial surge of testosterone levels (25). Patients should take anti-androgens prior to and for the first 2-4 weeks of therapy with GnRH agonists to cover the initial flare. It takes approximately 4-8 weeks for GnRH analogues to reach testosterone castration levels within the desired target range (24).

Castration can be achieved in a surgical or medical manner. The target of castration is to lower testosterone levels to less than 50 ng dl⁻¹ and in practice levels of below 20 ng dl⁻¹ are usually attained (24). Surgical castration via bilateral surgical orchiectomy attains similar results to ADT because it directly removes the major source of androgen production (5). However, contemporary practice demonstrates that GnRH agonists are the preferred castration method and are the standard of long-term hormonal therapy (24). This can be attributed to their ease of administration and their reversibility. Moreover, patients are more likely to favour such medical therapy because of the emotional and psychological impact associated with surgical castration (25).

1.9 Adjuvant and salvage radiotherapy after radical prostatectomy

Adjuvant radiotherapy is used 1-6 months following radical prostatectomy in the absence of any signs of recurrence and involves applying radiotherapy to the prostate bed, the seminal vesicle bed and to the area of pelvic lymph nodes. Adjuvant radiotherapy has been shown to reduce the risk of biochemical recurrence and significantly improve the metastasis-free survival (26).

Salvage radiotherapy, on the other hand, is initiated when there are signs of biochemical recurrence post-prostatectomy following a period of early surveillance of PSA to detect any disease progression (27).

Adjuvant radiotherapy was favoured over salvage radiotherapy for use in high-risk patients to reduce the risk of biochemical recurrence and death whilst improving the clinical-recurrence free survival. Patients with a high-risk profile may profit more from adjuvant therapy rather than surveillance followed by salvage therapy. Salvage radiotherapy however, has been shown to provide a comparable survival benefit to adjuvant radiotherapy and may be essential in the prevention of patient overtreatment (27).

1.10 Treatment of metastatic prostate cancer

Worldwide, prostate cancer represents the most commonly diagnosed cancer and is the sixth principle cause of cancer-related death (28). In the European Union (EU) alone, more than 70,000 men die of prostate cancer every year (29).

Prostate cancer initially presents as castration-naïve before transitioning to the fatal castration-resistant phenotype. Androgen deprivation is the cornerstone of treatment at the initial castration-naïve stage and is achieved with androgen deprivation therapy (ADT), orchiectomy or a combination of the two (24).

In newly diagnosed castration-naïve metastatic prostate cancer, the early administration of docetaxel chemotherapy or abiraterone acetate at the time of first-line long-term hormone therapy is associated with increased overall survival (OS). In clinical trials, the addition of docetaxel to ADT increased median survival by 10 months when compared to ADT alone. Therefore, men who are fit enough to receive chemotherapy should have docetaxel added to the standard of care (30). Abiraterone acetate, an inhibitor of the CYP17A1 enzyme involved in the intracellular production of androgens (31), also demonstrated an increase in OS when combined with ADT compared to ADT use alone. In clinical trials, a 37% increase in overall survival (OS) was reported in the combination group. Consequently, abiraterone acetate should likewise be considered for use alongside hormone therapy in this subset of patients (32).

In the majority of patients, ADT keeps disease under control for only 12 to 18 months before advanced prostate cancer inevitably becomes castration resistant (33).

Castration-resistant prostate cancer is defined as disease progression biochemically or radiologically despite levels of testosterone below 50 ng per decilitre (1.7 nmol per litre). According to guidelines from the European Association of Urology, biochemical progression is defined as "three consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir, and a PSA of more than 2 ng/mL." Radiological progression, on the other hand, is "the appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumors)." Symptomatic progression itself is not sufficient for a diagnosis of CRPC and must subsequently be followed up by further investigation (7).

The castration-resistant state is invariably fatal and typically leads to death within 24 to 48 months following its onset (34). The therapeutic armamentarium available today has allowed for extension of patient survival via the use of six indispensable treatments. Among these are: the taxanes- docetaxel and cabazitaxel; novel androgen receptor (AR) pathway inhibitors- abiraterone acetate and enzalutamide; and bone targeting alpha emitting radionuclide- Radium 223 chloride. The addition of these therapies to our arsenal in the fight against prostate cancer has ameliorated outcomes and has led to increased overall survival and health-related quality of life alongside other parameters (35).

In castration-resistant prostate cancer, the use of enzalutamide and abiraterone acetate has been shown to increase overall survival before and after the use of chemotherapy agents (40,41).

Enzalutamide was initially approved for use in mCRPC post-docetaxel therapy in 2012. However in 2014, its usage was extended to chemotherapy-naïve patients (36). Enzalutamide works by competitively binding to the ligand binding domain of the androgen receptor. Pre-chemo use of enzalutamide in comparison to placebo resulted in an 81% reduction of radiographic progression and a 29% decrease in the risk of death. Moreover, enzalutamide improved quality of life and delayed the need for cytotoxic chemotherapy (28).

Similarly, abiraterone acetate was shown to be of significant benefit in chemotherapy-naïve mCRPC. Radiological progression free survival (rPFS) and OS were increased when compared with placebo. There was a significant improvement in rPFS in the abiraterone group of 16.5 months compared with 8.3 months in the prednisone alone group. Moreover, patients who received abiraterone with prednisone had a 25% decreased risk of death (34).

The use of AR-targeted therapies before chemotherapy is fundamental in CRPC treatment. To date, enzalutamide and abiraterone acetate are the only oral treatments approved in the treatment of mCRPC. On the other hand, docetaxel and cabazitaxel are intravenous chemotherapies which require administration at the hospital and are associated with many adverse events. As such, prophylactic measures and a high degree of caution should be maintained during chemotherapy. As standard practice, oral therapies are prescribed first in most mCRPC and when signs of progression are detected chemotherapy can be started if appropriate (37).

Chemotherapy used in mCRPC includes docetaxel and cabazitaxel. Docetaxel, which was approved for use in 2004, is associated with increased survival and is the first line chemotherapy agent in mCRPC (38). In the case of docetaxel-resistant mCRPC, cabazitaxel is the second line chemotherapy treatment. Cabazitaxel is a tubulin-binding taxane drug which is just as potent as docetaxel and is the first drug to improve survival in this setting (39).

In the post chemotherapy space, various medications have been used including abiraterone acetate and enzalutamide. Two large phase III trials, COU-AA-301 and AFFIRM, confirmed significant benefit with post-chemotherapy use of abiraterone acetate and enzalutamide respectively. Both trials were eventually unblinded considering the success of the treatments and patients were allowed to crossover and receive treatment instead of placebo if they met the criteria (40,41).

The COU-AA-301 trial demonstrated improved survival when abiraterone acetate was used post-chemotherapy in mCRPC patients. Abiraterone plus prednisone reduced the risk of death by 35.4 % and increased overall survival by 3.9 months in comparison to placebo plus prednisone. Besides increasing overall survival, abiraterone acetate was superior to placebo with respect to PSA response rate, time to PSA progression, median rPFS and objective response rate according to the RECIST criteria in patients with measurable disease at baseline (40). Adverse events associated with abiraterone acetate are linked to the increased production of mineralocorticoids following CYP17 blockade. This includes fluid retention, edema, hypokalemia and hypertension (36). Other second-line hormonal agents do not increase OS and have less favorable safety profiles when compared to abiraterone acetate. On the whole, abiraterone acetate was associated with a good compliance and its toxicity was mainly related to mineralocorticoid overproduction which could easily be reversed via the use of prednisone (40).

The AFFIRM trial showed a prolongation of survival with post-chemotherapy enzalutamide when compared to placebo. Enzalutamide increased OS by a median of 4.8 months and reduced the risk of death by 37%. Moreover, enzalutamide was significantly superior to placebo in all of the defined secondary end points: PSA-level response rate, soft-tissue response rate, FACT-P quality-of-life-response, the time to PSA progression, rPFS and the time to first SRE. Further to this, adverse events of grade 3 or above were less frequent in the enzalutamide group and the median time to adverse events with enzalutamide was 12.6 months compared to 4.2 months with placebo. However, a higher incidence of all grades of fatigue, diarrhea, hot flushes, musculoskeletal pain, and headache was reported in the enzalutamide group (41). Enzalutamide should be administered with care because it can provoke seizures in a small percentage of patients particularly those who are predisposed to having a seizure (28). This includes patients with a history of seizures, underlying brain injury, stroke, brain metastases, alcoholism or the use of other medications that lower seizure threshold. Therefore, enzalutamide is not suitable for use in this particular subset of patients. Overall, enzalutamide is an indispensable therapy for use post-chemotherapy because it prolongs survival and is well tolerated due to its favourable side effect profile (41).

Prostate cancer has a predilection to metastasise to bone tissue and more than 90% of patients with mCRPC are found to have such metastases. This has several severe consequences including disability, decreased quality of life, increased treatment costs and even death. In contrast to other types of cancer, the majority of prostate cancer deaths are due to bone disease and its associated complications (42).

Approximately 20-40% of patients with mCRPC and bone metastases do not receive chemotherapy because they are too frail (ECOG >2), have coexisting conditions or do not wish to have chemotherapy. The use of Ra-223 addresses this important group of patients (42). Radium-223, an alpha emitter, has been shown to increase survival and reduce skeletal related events whilst having minimal adverse effects on surrounding healthy tissue. Ra-223 was approved for use in 2013 for mCRPC with symptomatic bone metastases but no known visceral involvement (43).

2. OBJECTIVES

To retrospectively compare the efficacy of abiraterone acetate and enzalutamide in the treatment of patients with mCRPC in the post-docetaxel setting outside of randomised clinical trials and in real clinical practice. This was measured in terms of biochemical, radiological and clinical progression free survival (i.e. bPFS, rPFS and cPFS, respectively) and OS in 58 consecutive patients in a single institution. We also evaluated the toxicity of both agents.

3. MATERIALS AND METHODS

In this retrospective cohort study data was collected from patients' charts in the Department of Oncology and Radiotherapy in Split. A total of 58 consecutive mCRPC patients (n=58) treated with abiraterone acetate (1000 mg/day, 1h before or 2h after meal) plus prednisone (2x5 mg) (n=27) and enzalutamide (160 mg per day) (n=31) from October 2015 until May 2018 in the post-docetaxel setting were included in this study.

All patients had castrate levels of serum testosterone (< 50 ng/dl or 1.7 nmol/l). Patients were treated until there was progression of disease or unacceptable toxicity. In order to stop treatment, two out of three criteria for progression (i.e. biochemical, radiological or clinical) should be fulfilled. For each cycle patients were evaluated for toxicity, biochemical progression with PSA and clinical progression. Patients were evaluated every three cycles for radiological progression with bone scintigraphy, abdominal/ pelvic CT or ultrasound and chest X-ray using RECIST criteria (Response Evaluation Criteria in Solid Tumors) and PCWG-2 criteria (Prostate Cancer Working Group) for bone metastases progression.

Statistical analysis was performed using descriptive statistics by means of Microsoft Excel and SPSS 16.0 software packages. For survival analysis, the Kaplan-Meier method was used. To prove the probability of null hypothesis accuracy, a t-test with a confidence interval of 95% was used and a p value ≤ 0.05 was considered statistically significant.

4. RESULTS

Table 4. Patients' characteristics with abiraterone acetate (AA+P) or enzalutamide (ENZ) treatment.

Characteristics		Treatment (n=58)	
		AA+P (n=27)	ENZ (n=31)
Age, months (median)		71	72
Gleason score, n, (%)	3+3	2 (7)	9 (29)
	3+4	8 (30)	5 (16)
	4+3	5 (18)	6 (19)
	8-10	12 (44)	11(35)
	Unknown	1 (3)	1 (3)
Initial stage, n (%)	Localized	7 (26)	12 (38)
	Metastatic	20 (74)	20 (62)
Duration of response to first ADT, months (median)		17	26
Site of metastases, n (%)	Bones	11 (41)	18 (58)
	Lymph nodes (LN)	4 (15)	2 (6)
	Bones + LN	6 (22)	9 (29)
	Visceral +/- other	3 (11)	4 (13)
Previous lines of hormonal treatment, n (%)	1	10 (37)	12 (38)
	2	13 (48)	15 (48)
	3	4 (15)	5 (16)
	4	0 (0)	1 (3)
Duration of response to docetaxel, months (median)		9	8
Type of progression on docetaxel,%	Biochemically (B)	6 (22)	8 (26)
	Radiologically (R)	0 (0)	1 (3)
	B+R+Clinically (C)	4 (15)	9 (29)
	B+R	12 (44)	9 (29)
	B+C	4 (15)	3 (9)
	R+C	0 (0)	4 (13)
ECOG status	0	11 (41)	9 (29)
	1	13 (48)	16 (52)
	2	3 (11)	7 (23)
Symptoms (bone pain according to VAS-scale), n (%)	Asymptomatic	9 (33)	7 (23)
	Mildly symptomatic	16 (59)	16 (52)
	Symptomatic	2 (7)	9 (29)

The median follow up time in this study was 12.8 months and the data cut-off point was May 15th 2018. The median duration of therapy was 6 months for patients treated with AA+P, and 7 months for patients treated with ENZ.

OS was not reached (NR) for AA+P patients and was 24 months for ENZ patients, $P=0.6878$ (Figure 1).

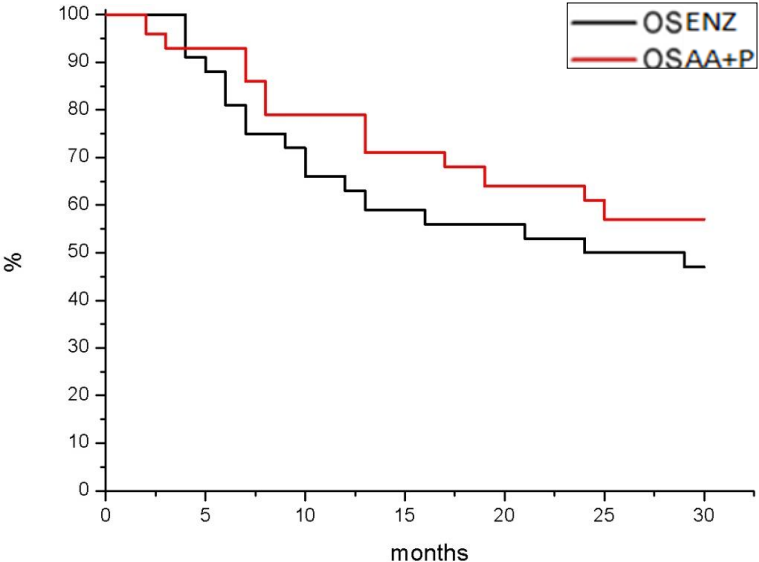


Figure 1. – Kaplan-Meier curves for OS.

bPFS was 8 months for AA+P patients and 5.5 months for ENZ patients, $P=0.6153$ (Figure 2).

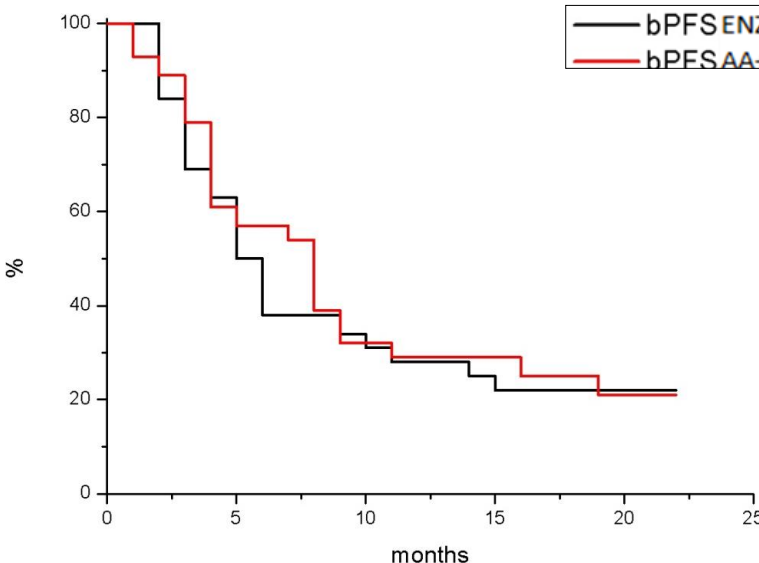


Figure 2. – Kaplan-Meier curves for bPFS.

rPFS was 11.5 months for AA+P patients and was 8 months for ENZ patients, $P=0.2692$ (Figure 3).

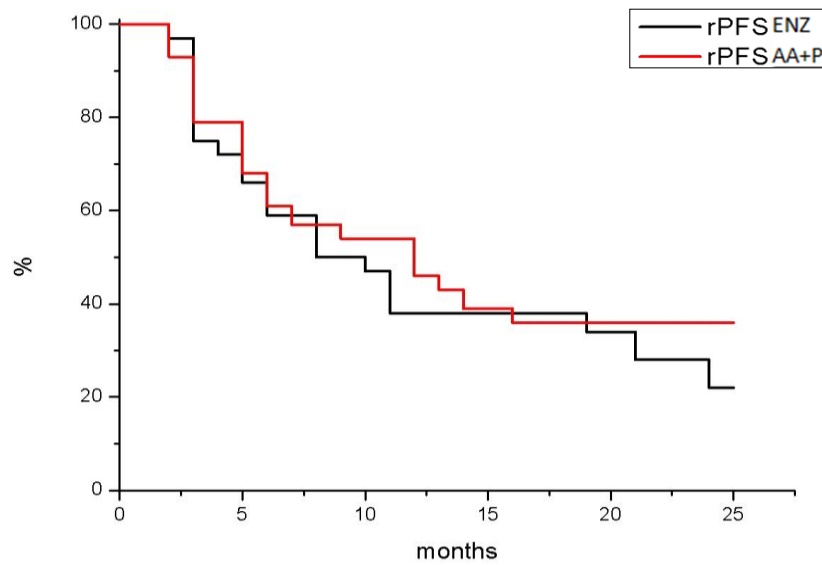


Figure 3. – Kaplan-Meier curves for rPFS.

cPFS was 15 months for AA+P patients and was 13 months for ENZ patients, $P= 0.5592$ (Figure 4).

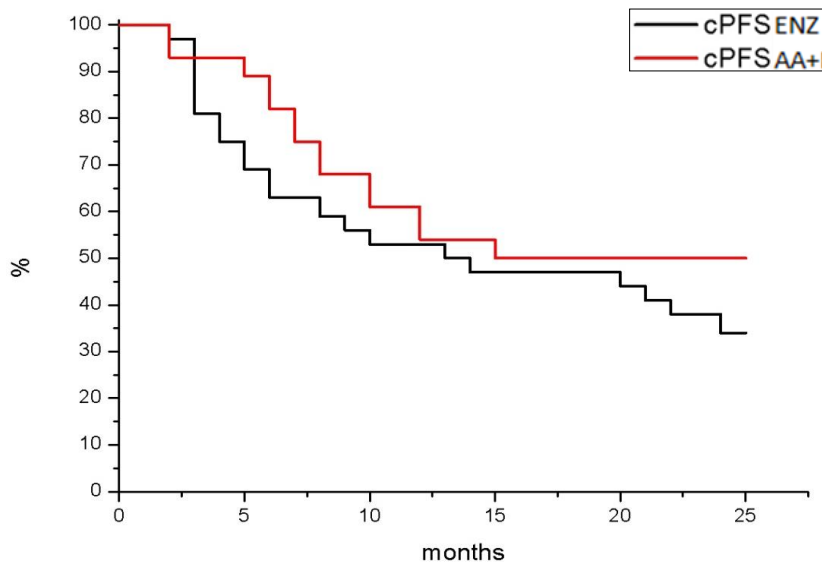


Figure 4. – Kaplan-Meier curves for cPFS.

Table 5. Toxicity recorded in patients' charts.

Adverse event		AA+P (n=27)	ENZ (n=31)
Vertigo,n (%)	Gr I	1 (4)	2 (6)
Back pain,n (%)	Gr I	1 (4)	0 (0)
	Gr II	1 (4)	0 (0)
Fatigue,n (%)	Gr I	7 (26)	0 (0)
	Gr II	2 (7)	4 (13)
Bone pain,n (%)	Gr I	8 (30)	9 (29)
	Gr II	3 (11)	5 (16)
Anemia,n (%)	Gr I	3 (11)	3 (10)
	Gr II	2 (7)	3 (10)
Thrombocytopenia,n (%)	Gr I	3 (11)	0 (0)
	Gr II	0 (0)	1 (3)
Fever,n (%)	Gr I	1 (4)	1 (3)
	Gr II	1 (4)	0 (0)
Decreased appetite, n (%)	Gr I	1 (4)	2 (6)
	Gr II	0 (0)	1 (3)
Hypokalemia, n(%)	Gr I	2 (7)	0 (0)
Lower leg edema, n (%)	Gr I	1 (4)	0 (0)
	Gr II	1 (4)	0 (0)
Elevated liver enzymes	Gr I	1 (4)	0 (0)
	Gr II	0 (0)	2 (6)
Nausea	Gr I	2 (7)	0 (0)
Vomiting	Gr I	2 (7)	0 (0)
Diabetes mellitus	Gr I	1 (4)	0 (0)
Hyperbilirubinemia	Gr I	1 (4)	2 (6)
Cognitive disorder	Gr I	0 (0)	2 (6)
Hypertension	Gr II	1 (4)	0 (0)
Diarrhea	Gr II	0 (0)	1 (3)

5. DISCUSSION

The objective of this small retrospective analysis was to obtain information about the efficacy and toxicity of two relatively new and expensive drugs abiraterone acetate plus prednisone and enzalutamide (AA + P and ENZ) in the treatment of our 58 mCRPC patients in the post-docetaxel setting. This was done with unselected patients in real clinical practice and provides data about these agents beyond randomized clinical trials.

Despite the numerical difference in mOS, bPFS, rPFS, cPFS, in this relatively small number of patients, there was no statistically significant difference found between the two groups. From these results the conclusion is that both drugs were equally effective in our mCRPC patients in the post- docetaxel setting.

If we compare the results of mOS in our groups of mCRPC patients with the results of the most important randomized trials for AA + P (i.e. COU-AA 301) and ENZ (i.e. AFFIRM), it shows that the results of our patients' treatment with these agents were even better. Namely, in the COU-AA 301 study, mOS was 14.8 months (40) while in our mCRPC patients treated with AA+P mOS was not reached. In the AFFIRM trial, mOS was 18.4 months (41) whereas in our mCRPC patients treated with ENZ mOS was 24 months.

In other observed parameters such as bPFS (8.0 months for AA + P and 5.5 months for ENZ) or rPFS (11.5 months for AA + P and 8.0 months for ENZ) we achieved comparable results to the COU-AA 301 trial (10.2 or 5.6 months, respectively) (40) and the AFFIRM study (8.3 and 8.3 months, respectively) (41).

Regarding the observed toxicity in our population of patients, the incidence of certain side effects (among other typical side effects for each drug) did not differ significantly from those observed in the randomized trials mentioned above (40,41). Moreover, most of the recorded side-effects were of grade I or II. This is incredibly important in this patient population who have a limited survival. This is not only because it allows for extension of overall survival but also because quality of life can be maintained with such therapies due to favourable toxicity profiles.

The main limitation of the present study was the small sample size of patients which limits the utility of such data on a universal basis. However, despite the small sample size, results of a comparable nature to previously conducted larger trials were obtained. With respect to this, it is clear to see that both ENZ and AA provide significant benefits for patients in terms of mOS, bPFS, rPFS, cPFS in Split. In order to address this particular limitation on a larger scale, future research on a greater subset of patients in Split would be very interesting and provide a further comparison.

A particular strength of this study was the fact that it was conducted outside of clinical trials. This reflects the efficacy of such treatments in patients in the setting of real clinical practice and highlights the importance of the analysis of expensive therapy in low and middle income countries.

6. CONCLUSION

In conclusion, AA + P and ENZ represent an effective form of treatment for patients with mCRPC. Both drugs prolong survival, time to biochemical and radiological progression for patients at this stage of disease with acceptable toxicity profiles for both agents.

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8. SUMMARY

Title: A RETROSPECTIVE STUDY COMPARING ABIRATERONE ACETATE AND ENZALUTAMIDE IN THE TREATMENT OF PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER IN SPLIT

Objectives: To retrospectively compare the efficacy of AA and ENZ in the treatment of patients with mCRPC in the post-docetaxel setting in terms of biochemical, radiological and clinical progression free survival (i.e. bPFS, rPFS and cPFS, respectively) and OS in 58 consecutive patients in a single institution. We also evaluated the toxicity of both agents.

Methods: A retrospective cohort study using the data collected from patients' charts in the Department of Oncology and Radiotherapy in Split. A total of 58 consecutive mCRPC patients (n=58) treated with AA (1000 mg/day, 1h before or 2h after meal) plus P (2x5 mg) (n=27) and ENZ (160 mg per day) (n=31) from October 2015 until May 2018 in the post-docetaxel setting were included in this study.

Results: Despite the numerical difference in mOS, bPFS, rPFS, cPFS, in this relatively small number of patients, there was no statistically significant difference found between the two groups of patients.

In comparison to the most significant randomised control trials for AA + P (COU-AA 301) and ENZ (AFFIRM), the results of our patients' treatment with these agents regarding mOS were even better. Namely, in the COU-AA 301 study, mOS was 14.8 months (40) while in our mCRPC patients treated with AA+P mOS was not reached. In the AFFIRM trial, mOS was 18.4 months (41) whereas in our mCRPC patients treated with ENZ mOS was 24 months. In other observed parameters such as bPFS or rPFS we achieved comparable results to the COU-AA 301 trial and the AFFIRM study (40,41).

Regarding the observed toxicity in our patients, the incidence of certain side effects (among other typical side effects for each drug) did not differ significantly from those observed in the randomized trials mentioned above.

Conclusion: In conclusion, AA + P and ENZ represent an effective form of treatment for patients with mCRPC. Both drugs prolong survival, time to biochemical and radiological progression for patients at this stage of disease with acceptable toxicity profiles for both agents.

9. CROATIAN SUMMARY/ SAŽETAK

Naslov: RETROSPEKTIVNA STUDIJA USPOREDBE ABIRATERON ACETATA I ENZALUTAMIDA U LIJEČENJU BOLESNIKA S METASTATSKIM KASTRACIJSKI REZISTENTNIM RAKOM PROSTATE U SPLITU

Ciljevi: Retrospektivno usporediti djelotvornost AA i ENZ u liječenju pacijenata s mCRPC nakon progresije pod docetakselom u smislu biokemijskog, radiološkog i kliničkog preživljavanja bez progresije (tj. BPFS, rPFS i cPFS) i OS u 58 uzastopnih pacijenata u jednoj ustanovi. Također smo procijenili toksičnost oba lijeka.

Metode: Retrospektivna kohortna studija pomoću podataka prikupljenih iz povijesti bolesti bolesnika u Klinici za onkologiju i radioterapiju u Splitu. Sveukupno 58 bolesnika s mCRPC (n = 58) koji su liječeni s AA (1000 mg / dan, 1h prije ili 2h nakon obroka) plus P (2x5 mg) (n = 27) i ENZ (160 mg dnevno) (n = 31) od listopada 2015. do svibnja 2018. nakon progresije pod docetakselom uključeni su u ovu studiju.

Rezultati: Unatoč brojčanim razlikama u mOS, bPFS, rPFS, cPFS, s relativno malim brojem pacijenata, nije pronađena statistički značajna razlika između dviju skupina bolesnika. U usporedbi s najznačajnijim randomiziranim studijama za AA + P (COU-AA 301) i ENZ (AFFIRM), rezultati našeg liječenja bolesnika s navedenim lijekovima u medijanu OS bili su još bolji. Naime, u studiji COU-AA 301, mOS je iznosio 14,8 mjeseci (40) dok kod naših mCRPC bolesnika liječenih AA + P mOS nije postignut. U ispitivanju AFFIRM, mOS je iznosio 18,4 mjeseci (41), dok je kod naših mCRPC bolesnika liječenih ENZ mOS iznosio 24 mjeseca. U drugim promatranim parametrima kao što su bPFS ili rPFS postigli smo usporedive rezultate s ispitivanjem COU-AA 301 i AFFIRM (40,41).

Što se tiče promatrane toksičnosti kod naših bolesnika, učestalost određenih nuspojava (među ostalim tipičnim nuspojavama za svaki lijek) nije se značajno razlikovala od onih promatranih u gore spomenutim randomiziranim istraživanjima.

Zaključak: AA + P i ENZ predstavljaju učinkovit oblik liječenja bolesnika s mCRPC. Oba lijeka produljuju preživljavanje, vrijeme do biokemijske i radiološke progresije pacijenata u ovoj fazi bolesti s prihvatljivim profilom toksičnosti za oba lijeka.

10. CURRICULUM VITAE

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I am a highly motivated individual who strives to continuously enhance skills and gain knowledge. Alongside my studies I have maintained a love for playing musical instruments, languages and sport.