



EVALUATION OF THE PROGNOSTIC LEVEL OF PSA IN PATIENTS WITH PROSTATE CANCER UNDERGOING ORCHIECTOMY AND DRUG THERAPY

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ARTICLE INFO

Article History:

Received 6th January, 2020
Received in revised form 15th
February, 2020
Accepted 12th March, 2020
Published online 28th April, 2020

Key words:

Prostate Cancer; Hormonal Therapy;
Drug Therapy; Orchiectomy;
Androgen-Deprivation Therapy

ABSTRACT

Objective: Prostate cancer is one of the most prevalence cancers in male and common cancer in the world. There are two main methods for control the prostate cancer but orchiectomy is highly effective for decreasing level of testosterone but some patients refused this method and been replaced by different forms of medical castration, often referred to as androgen-deprivation therapy (ADT). **Materials and Methods:** This systematic review was conducted based on the PRISMA checklist. Articles were extracted with selected keywords from the PubMed, SID, Springer, Medlib and Since Direct databases without any language restrictions. 100 articles were identified and after removal of unrelated or repetitive articles, 54 articles were selected. **Results:** Researches are ongoing to find out the way or better strategies to eliminate the adverse effects. Early detection of prostate cancer deaths is possible. Now, with new information and new therapeutic patterns, a high percentage of patients with prostate cancer have been able to fully recover. **Conclusions:** Many treatment modalities are important in the treatment of prostate cancer, but what is important to us in this research work is to compare the recurrence of the disease between the two groups of orchiectomies and drug treated patients with PSA levels that appear PSA increases later in the orchiectomy group.

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INTRODUCTION

Statistical data and clinical symptoms the mortality rate of prostate cancer is indicative of three broad spectrum of the disease's progression. Prostate cancer can grow slowly and has a long period of clinical symptoms.

In other cases, the tumor grows rapidly and tumor invasion can be made to other tissues. In such cases, the time interval between the onset of the disease and the extent of its extension is very short. Between these two growth ranges, there are tumors with a moderate rate of growth Prostate cancer appears with symptoms associated with urination or abdominal pain.

Prostate cancer is one of the most prevalence cancers in male and common cancer in the world. However rates of detection of prostate cancers are wide across the world, with Europe and the United States detecting higher frequency than South and East Asia. Prostate cancer is also cause of cancer death after lung and bronchus cancer in USA mortality¹. Androgen deprivation therapy (ADT) is widely used to detection of the symptoms of advanced prostate cancer and has shown to slow the progression of the disease². ADT is the established treatment of metastatic prostate cancer has different approaches in the reduction of androgen activity rate include surgical castration (bilateral orchiectomy) and medical castration (luteinizing hormone-releasing hormone agonists/antagonists) [LHRH] which are found to be equally

effective. The bilateral orchiectomy is an effective method of rapidly decreasing testosterone levels. It is a simple procedure with minor surgical risks and physical morbidity; however, it has fallen out of favor given its physiological impact and the availability of viable medical alternatives for androgen deprivation³.

Without screening, many cases of prostate cancer do not ever become clinically evident. Prostate cancer often grows slowly that most patients die of other causes before any sign and disease alarms and becomes clinically advanced disease related to men without any prognosis^{4,5}.

While orchiectomy is highly effective for decreasing level of testosterone and the procedure is unacceptable to many patients and has now largely been replaced different forms of medical castration, often referred to as androgen-deprivation therapy (ADT). The most common agents used for ADT are Gonadotropin-releasing hormone (GnRH) receptor agonists that achieve the desired therapeutic goal (serum testosterone \geq 0/5ng/ml) in 90 -100% of patients, but only after a period of 7–28 days and an initial surge of testosterone level^{6,7}. This initial surge may stimulate prostate cancer cells in progressive and metastatic cases; therefore, it leads to an exacerbation of clinical symptoms, including spinal cord compression, bone pain and urethral barrier that usually painful for patients in urination time⁸. However, chemotherapy, hormonal therapy,

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cryosurgery, and high intensity focused ultrasound (HIFU) are also belonging to the treatment strategies, depending on clinical conditions, and outcomes.

Also, the choice of treatment depends on the stages of the disease progression, the level of prostate specific antigen (PSA), the Gleason score among others. Patient's age, general health conditions, his interest about treatments, and their possible side-effects may also influence choosing among different treatment options. Any of the treatments may have significant side-effects, so the treatment discussions often focus on balancing the goals of therapy with the risks of lifestyle alterations. Patients with prostate cancer are also recommended to work side by side with their doctors, and use a combination of the treatment for their prostate cancer⁹. The optimal management of prostate cancer still remains controversial.

Etiology: Prostate Carcinogenesis

The cause of prostate cancer is still unknown, but statistical and clinical studies link the risk of prostate cancer to malignancy:

Age: Prostate cancer is most commonly seen in older people and people under the age of 50 are rarely affected. Men over the age of 60 are more at risk for prostate cancer and should be more aware of the warning signs of the disease.

Genetic Factors: Hereditary history of prostate cancer is an important factor in developing this cancer. A history of prostate cancer among close family members, including a father and a brother, increases the likelihood of having it.

Hormonal Factors: Steroid hormones (testosterone and androgens) play an important role in the growth and maintenance of normal function in adult men. Increased levels of testosterone in the blood often accelerate the process of prostate cancer malignancy.

Nutrition: Diet has the potential to prevent or prevent the development of prostate cancer. Scientific studies have shown that vegetables containing significant amounts of vitamin C and E, especially tomatoes, are considered to be protective against prostate cancer, while the use of high levels of animal fat is a predisposing factor in prostate cancer.

Chemicals: Contact with carcinogenic chemicals in the environment, such as cadmium, which is used in the manufacture of some alloys and batteries, is a predisposing factor in the development of prostate cancer.

Sexually Transmitted Diseases: The presence of sexually transmitted diseases increases the likelihood of prostate cancer.

Patterns of Prostate Cancer Screening

Digital rectal examination is one of the patterns of prostate cancer screening. In this way, the doctor examines the prostate gland through the patient's rectum. The rough and irregular surface of the tissue is one of the warning signs of prostate cancer. Cancer tumors produce specific antigens that can be detected by blood tests. The antigen produced entirely by the prostate gland is the Prostate Specific Antigen (PSA). Rapid detection of prostate cancer by measuring prostate-specific antigen is one of the screening tests. In patients with prostate cancer, the level of this antigen is higher.

Of course, only the level of PSA in a person's blood test does not indicate prostate cancer. In some cases, infection or

"benign enlargement" of the prostate gland can increase PSA levels in the blood. Early detection of the disease adds at least 5 years to the lives of those with prostate cancer. It is recommended that men over the age of 4 years undergo a prostate gland through a rectal examination and that they perform a prostate-specific antigen test every year over the age of 6 years.

Treatment of Prostate Cancer

Depending on the patient's condition, one or more of these patterns may be prescribed:

Monitoring the Disease: In this way the patient is closely monitored by the physician, without any treatment pattern applied. This method is prescribed for patients who do not benefit from surgery, or that their prostate cancer growth is slow and slow and will not adversely affect their health in the long run.

Surgery: Complete removal of the prostate gland (Prostatectomy).

Cryotherapy: Therapeutic use of severe cold. In this way the catheter(probe) the ultrasound is inserted into the rectum so that the physician can see the image of the desired location on the screen. In this way, the doctor directs liquid nitrogen into the prostate by inserting a catheter into the prostate gland through a small gap between the anus and the scrotum containing the testicles. Liquid nitrogen inside the tissue results in the freezing of tissue and the destruction of cancer cells in the prostate gland. Cryotherapy is an effective way to treat small sections of cancer. Bladder damage and inflammation of the genitalia are side effects of this procedure.

Chemotherapy: The use of chemical drugs results in the destruction of cancer cells. Side effects of chemotherapy include head and eyebrow loss, decreased white blood cell count, weakened immune and immune system, infection, pain, dry mouth and osteoporosis.

Radiotherapy: Since the tumor may encompass the tissues around the prostate gland, surgery and resection of the prostate gland is not sufficient, and any manifestation of PSA in the test indicates the extent of the tumor. In this situation, broader treatment patterns such as radiotherapy are followed.

External Radiotherapy: In this way the patient is exposed to radiation. This procedure is completely painless and lasts for 1 to 2 weeks. But the patient reports side effects such as anal irritability, diarrhea, and excessive fatigue caused by radiation. Nausea, vomiting, anorexia, and vascular and respiratory injuries can be other side effects of radiation therapy. Radiation therapy may also suppress the hematopoietic system, reduce white blood cells, weaken the immune system, and eventually lead to infection.

Internal Radiotherapy or Brachy Therapy: Brachy therapy is for direct delivery of large amounts of radiation to a malignant lesion. In this way, the patient is implanted in the operating room using thin strips of ionized material.

Hormone Therapy: Because testosterone helps to develop prostate cancer, the goal of hormone therapy is to reduce sex hormones in the body. The procedure is performed with the use of anti-testosterone drugs and involves the administration of estrogen as a pill that has an anti-testosterone effect. Side effects of taking estrogen-containing pills include pain in the

breast and breast growth that can be eliminated by discontinuing the pill.

Early detection of prostate cancer deaths is possible. Today, with new information and therapeutic patterns, a high percentage of patients with prostate cancer have been able to fully recover.

This review article represents that Patients who received Orchiectomy had a longer duration than those in the other group than those who received hormone therapy or drug treatment. In this study, we included these patients receiving hormone therapy but excluded patients on radiotherapy or chemotherapy for prostate.

Table 1 Prostate Cancer Staging Systems (TNM)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	No palpable tumor—not evident by imaging
T1a	Tumor incidental histological finding in 5% or less of tissue resected
T1b	Tumor incidental histological finding in more than 5% of tissue resected
T1c	Tumor identified by prostate needle biopsy due to elevation in PSA
T2	Palpable tumor confined to the prostate
T2a	Tumor involves one half of one lobe or less
T2b	Tumor involves more than half of one lobe, but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostatic capsule
T3a	Extra capsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, pelvic wall, NX Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Main Text

Hormonal Therapy

Early-Stage Prostate Cancer

Hormone therapy is usually prescribed for patients suffering early-stage prostate cancer with high to intermediate risk of relapse after radiotherapy (either during or before it) or after prostate resection (prostatectomy)^{10, 11}. Some elements, such as the degree of tumor determined by Gleason Score, the amount of tumor expanded to adjacent tissues and whether or not it has reached the lymph nodes determine whether the cancer is recurrent. According to the risk of recrudescence, the length of hormonal treatment varies from 6 months (for intermediate risk) to 24-28 months (for high risk)¹².

The result of concurrent treatment with hormone therapy and external radiation beam therapy is much better in both life expectancy and recurrence than radiotherapy alone^{5, 13}. A better outcome was observed in those who received hormone therapy with Surgical castration¹⁴. Yet, the best time for Androgen Deprivation Therapy to go along with radiotherapy is not entirely clear¹⁵.

The researchers eventually determined that the most beneficial treatment was orchiectomy. In a study of 80 patients in Brazil, the treatment was hormone therapy and/or chemotherapy before surgical castration. The PSA range (30 to 45 days after surgery) measured between 1 to 3840 ng/ml and showed no survival benefit. Further investigations are ongoing to evaluate other severe ADT methods before prostatectomy¹⁶.

The level of PSA after surgery appears to be the best way to evaluate the survival rate. There is a tendency towards low PSA until sixth months after treatment^{17, 18}. Patients with a good response (high and long survival rate) after hormone therapy usually have PSA under 4 ng/ml in the first three months after the initial treatment¹⁹. When there is a PSA concentration less than 4 ng/ml, three months after treatment, the average time to disease progression is 30 months and the survival rate is over 36 months. With PSA greater than 4 ng/ml, the average time to disease improvement is about 18 months and the survival rate is 29 months.

Relapsed/Recurrent Prostate Cancer

Hormone therapy used alone is the standard treatment for men who have a prostate cancer recurrence as documented by CT, MRI, or bone scan after treatment with radiation therapy or prostatectomy. Therapy is sometimes recommended for men who have a "biochemical" recurrence—a rise in prostate-specific antigen (PSA) level following primary local treatment with surgery or radiation—especially if the PSA level doubles in fewer than 3 months and the cancer has not spread.

A randomized clinical trial among men with biochemical recurrence after prostatectomy found that men who had anti-androgen therapy plus radiation treatment were less likely to develop metastases or die from prostate cancer or overall than men who had placebo plus radiation²⁰. However, patients with lower PSA values did not appear to benefit from the addition of hormone therapy to radiation. Another recent clinical trial showed that for men with rising PSA levels after primary local therapy who were at high risk of metastasis but had no evidence of metastatic disease, adding chemotherapy with docetaxel to ADT was not superior to ADT in terms of several measures of survival²¹.

Advanced or Metastatic Prostate Cancer

Hormone therapy used alone is the standard treatment for men who are found to have metastatic disease (i.e., disease that has spread to other parts of the body) when their prostate cancer is first diagnosed¹². Clinical trials have shown that such men survive longer when treated with ADT plus abiraterone/prednisone, enzalutamide, or apalutamide than when treated with ADT alone¹². However, because hormone therapy can have substantial side effects, some men prefer not to take hormone therapy until symptoms develop.

The side effect of hormone therapy is loss tendency in sex, erectile dysfunction, loss of bone density, fracture of bones, loss of muscle mass, changes in blood lipids, insulin resistance, increasing of weight, fatigue, and growth of breast tissue¹³.

DISCUSSION

Considering that one theory could be that those who underwent surgery usually orchiectomy was more likely to recur and increase PSA levels than those who received medication or hormone therapy.

In 2009 Choueiri *et al.* had done a cohort study in which they studied 179 metastatic hormone-sensitive prostate cancer (HSPC) patients to investigate the relationship between the kinetics of PSA decline after androgen deprivation therapy (ADT) initiation and overall survival (OS) of patients. They had used the Dana-Farber Cancer Institute's (DFCI) institutional database. Their patients' PSA levels were

followed every three months. The patients were included to study who had metastatic HSPC and were treated with Androgen Deprivation Therapy (ADT).

Table 2 Quality Assessment of the included Study

Author	Year	No. of Patients	Country	Treatment	PSA Level	Follow Up	Results	Reference
Yamada et al.	2018	184	Japan	AW - AA - orchiectomy for high PSA levels	31% low 38% intermediate 31% high	32 Months	This study proved that a high PSA level was associated with favorable response to AW and AA therapies. Thus, serum PSA level was not associated with OS in metastatic prostate cancer.	14
Choueiri et al.	2009	179	USA	ADT	47 (median PSA)	4 Years	According to the results, they concluded any men with metastatic HSPC with a faster time of reaching to PSA nadir after ADT have shorter survival duration.	15
Tomioka et al.	2014	286	Japan	LHRH agonist, surgical castration, anti-androgen monotherapy or combined androgen blockade	174	47 Months	Their investigations revealed lower nadir PSA level and longer time from PADT to nadir were good for survival.	22
Ostergren et al.	2016	29	Denmark	LHRH agonist (Triptorelin)	61 µg/l	3 - 6 Months	The percentage of patients reaching nadir testosterone levels 87 %and 100% at 48 weeks (p <.05) in the sub capsular orchiectomyand triptorelin groups, respectively. After orchiectomy, Bold advantages of triptorelin in comparison with orchiectomy are the 29% higher percentage of men who had reached the lowest testosterone levels through triptorelin.	23
Nishiyama et al.	2014	Review article	Japan		92 µg/l		25% of BO cases had PSA level over 20 ng/dl and it has been proved degarelix is more effective than leuprolide in decreasing PSA level.	24
Parmaret al.	1987	49	UK	BO	14.24+- 0.64 nmol/l(mean testosterone)	3 Month	Their results showed Triptorelin is an effective alternative for orchiectomy.	25
		55		Triptorelin	13.35+-0.93 nmol/l(mean testosterone)			
		144		BO	11.09 nmol/L (mean testosterone)			
Kaisaryet al.	1991	148	UK	Zoladex	12.46 nmol/L (mean testosterone)	2 Years	2 year follow up confirmed that Zoladex is an efficient alternative for orchiectomy in metastatic patients	26
		83		BO	366 (mean testosterone)			
Solowayet al.	1991	81	USA	Goserelin	363 (mean testosterone)	-	The results show that zoladex could be an alternative to orchiectomy in advanced prostate cancer.	27
							The results indicate that the effectiveness of orchiectomy as androgen withdrawal treatment in prostatic cancer should be assessed by measurement of both dihydrotestosterone and testosterone concentrations.	
Rohl et al.	1992	40	Denmark	BO	12.5 nmol/l (median total testosterone)	12 Month		28
Dijkeman et al.	1995	42 38	Netherlands	Goserelin 3.6 mg Goserelin 10.8 mg				29
Oefelein et al.	2000	35	USA	BO	-		The result indicates 3 months injections of LHRH agonist leads to 6 months testosterone levels about 0.2 ng/ml or less.	30
McLeod et al.	2001	180	USA	Abarelix 100 mg	350 ng/ml (median testosterone)	85 Days	Comparing with Leuprolide, Abarelix produced more and faster decrease in testosterone levels.	31
Chu et al.	2002	117	USA	Leuprolide 22.5mg		-	According to studies' outcome They concluded leuprolide acetate is doing well in decreasing testosterone level to < 50 ng/dl.	32
Perez-mareno et al.	2002	120	USA	Leuprolide 7.5mg		6 Month	The result indicates the influence of leuprolide acetate in testosterone suppression.	33
Sharifi et al.	2002	33 36	USA	Leuprolide 22.5 mg Leuprolide 7.5mg		-	They concluded that using leuprolide acetate provide stable decrease in serum testosterone.	34
Trachtenberg et al.	2002	168 83		Abarelix 100 mg Bicalutamide + Leuprolide		-		35

Abbreviations: AW, anti-androgen withdrawal; AA, nonsteroidal anti-androgen; ADT, androgen deprivation therapy; LHRH, luteinizing hormone-releasing hormone; BO, bilateral orchiectomy; PADT, primary androgen deprivation therapy.

Patient characteristics, PSA at ADT initiation, nadir PSA, time to PSA nadir (TTN), and PSA decline (PSAD) in relation to OS were analyzed. They followed up the patients for about four years. After starting ADT, the median OS was seven years, median PSA was 47, and PSA nadir was 0.28 ng/ml. According to the results, Choueiri *et al.* concluded that any men with metastatic HSPC with a faster time of reaching to PSA nadir after ADT have shorter survival duration¹⁵.

In another investigation by Ostergren *et al.* 58 patients who they were suffering from advanced prostate cancer, were considered for finding the differences between luteinizing hormone-releasing hormone agonist triptorelin (29 patients) and subcapsular orchiectomy (29 patients) in decreasing the serum testosterone levels. The group who were going to receive ADT had the mean age of 75, and the candidates for orchiectomy been about 72 years. Their PSA levels were 61 and 92 µg/l, respectively. Metastasis was observed in bone, regional lymph nodes, and visceral sites. The patients were followed up for 48 weeks. Doses of triptorelin were 22.5 mg through injections in 24 weeks. The method which used for assessing androgen levels was liquid chromatography-tandem mass spectrometry. They had checked testosterone levels after 12, 24, and 48 weeks after initiation of treatments. Nadir PSA level reached < 30 ng/dl after last follow up. The percentage of patients reaching nadir testosterone levels was 79% and 97% at 12 weeks (P < 0.05), 92% and 90% at 24 weeks (P = 0.73) and 87% and 100% at 48 weeks (p < 0.05) in the subcapsular orchiectomy and triptorelin groups, respectively. After orchiectomy, an increase in LH and FSH was observed while triptorelin suppressed them. Bold advantages of triptorelin in comparison with orchiectomy are the 29% higher percentage of men who had reached the lowest testosterone levels through triptorelin²³.

In a retrospective study, Lin *et al.* surveyed 121 patients with metastatic prostate carcinoma or whose tumor stage was over T3 and T4, between 2001 - 2006. 54 men received anti-androgen therapy (cyproterone, flutamide, bicalutamide) or LHRH agonist hormone therapy (goserelin, leuprorelin), and 67 of them underwent surgical castration. According to prognostic scores they sorted each medically or surgically castrated patient's two groups, good or poor prognostic groups. PSA check-up were performed every 3 months after initiation of therapies for two years. The primary PSA levels for surgery and drug receiving groups were 203 ng/ml and 298 ng/ml respectively.

Results show that the highest number of surgically castrated patients (72% of them) reached the PSA normalization rate (< 4ng/ml) in sixth month and for those who received drug therapies (55.5% of patients) the time is ninth month. During two years follow up no significant difference of PSA levels observed between the good prognosis sub groups, unrelatedly of therapeutic methods. While in poor prognostic groups, patients who underwent surgery showed better PSA normalization rate than those who received medical therapy³. This difference started since 18th month. During follow ups they recorded the PSA rebound (> 4 ng/ml or higher than last measurement). The main increase happened 1 year after treatments and at the end of second year the rate of PSA rebounding was considerably higher in medical castrated group (57% of patients) comparing surgically castrated group (25.4 % of patients)³⁶.

In 2015 Kitagawa *et al.* studied 2982 male with metastatic prostate cancer, which their data were gathered between 2001 and 2003 in J-CaP database and their therapy method was PADT. In this study, they compared clinical outcomes, including PSA levels in patients receiving two different therapeutic approaches; CAB (combined androgen blockade) (2101 patients) and non-CAB (881 patients)^{5,37}. CAB includes AA plus LHRH agonist or surgical castration. Non-CAB therapies include LHRH monotherapy (375 men), surgical castrations alone (190 men), AA alone (139 men) and LHRH plus short term AA (177 men). They measured PSA levels every three months during one year follow up, and initial PSA level for CAB group was 245 ng/ml, comparing non-CAB group (191 ng/ml), there was a significant difference between two groups (p= 0.008). Also, the PSA nadir levels showed notable differences among therapeutic methods, and it was lower in patients treated with CAB (0.3 ng/ml) versus non-CAB patients (1 ng/ml) and the p-value was <0.001³⁷.

In a retrospective research, at the west china hospital, Chen *et al.* studied different therapeutic approaches in two groups of advanced prostate cancer (stage 3 or 4) patients between 1996 and 2004³⁸. The first group consists of 300 cases who had been prescribed MAB (Maximal Androgen Blockade: the combination of castration and NSAAs), which 242 of them underwent bilateral orchiectomy plus flutamide and bicalutamide, and 58 patients received medical castration with flutamide and bicalutamide. The second group includes 308 patients who received only castration therapy, which 261 men of them underwent surgical castration, and the rest were prescribed medical castration³⁸. After primary evaluation of PSA levels, result was <50 ng/ml (cutoff value) in 284 patients and > 50 ng/ml for 324 men. The second PSA measurement conducted 3 months later, and PSA levels were decreased to < 4 ng/ml in 400 and > 4 ng/ml in 208 men. The statistical population of metastatic patients was 248 cases, 70% of those underwent MAB therapy, and 50% of other group got PSA normalization rate, and this result demonstrates the advantages of NSAAs and castration combination treatments for metastatic patient's therapy.

Grivas *et al.*³⁹ in his work suggest that patients with longer time to PSA > 9 months had longer survival in both lower and higher PSA nadir subgroups. In our study, even though patients with medical castration had a longer time to nadir PSA compared to surgical castration, the time to nadir was not greater than 9 months showing no correlation with the study of Grivas *et al.*³⁹ but in patients who had surgery therapy usually had a long time for recurrence PSA level because of due to several factors, such as removing an important factor such as a testicle which causes a high level of hormone secretion and exacerbates the disease, So our expectation is that a longer period of time is needed to keep the PSA level grows up.

Hormone therapy and orchiectomy became the effective treatment for men with metastatic prostate carcinoma. The initial regimen of androgen deprivation therapy included bilateral orchiectomy, estrogen therapy, or both. However, these therapies such as surgery in orchiectomy had a greatly negative impact on quality of life, not to mention the occurrence of lethal cardiac events⁴⁰. Releasing hormone agonists reduced the cardiac toxicity and the other side effects of ADT. In 1983 Labrie *et al.*⁴¹ reported a small series of patients with advanced prostate carcinoma managed with an LHRH analogue combined with an oral anti-androgen. In

addition, with the longer duration of LHRH dosage intervals and the reduced negative impact to patients' self-image and cosmetic appearance⁴², LHRH agonist therapy became more popular than surgical castration⁴³. Because medical castration is reversible and has less of a psychiatric impact than surgical castration, several new trials have been conducted in different clinical situations. These trials showed that patients with localized prostate carcinoma received no benefit from primary androgen deprivation therapy⁷; on the other hand, patients with metastatic prostate carcinoma showed a survival benefit with androgen deprivation therapy⁷. Restriction of medical expenses became inevitable and is an important factor in physicians' decision-making processes. As a result, the number of surgical castrations increased again^{44, 45}. As a result, in the poor prognosis group (>5 sites of bone metastasis, hydronephrosis, pain requiring analgesics, alkaline phosphatase >2 times the upper limit of the normal range), bilateral orchiectomy should be performed for a better survival benefit. The reason why surgical castration is superior to medical castration with LHRH is not clear but in our opinion PSA level usually grows up later than patients with LHRH agonist therapy.

There are some studies indicating that LHRH therapy does not achieve as low of a testosterone level as does bilateral orchiectomy^{10, 18, 46-48}. This might be one of the reasons why surgical castration had better outcomes for advanced prostate carcinoma, especially in the poor prognosis group. Another reason that might explain this difference is the sustainability of testosterone suppression. Bilateral orchiectomy would definitely cease the production of testosterone. Owing to different pharmacokinetics from person to person, the LHRH agonist might not be able to remain effective for one full month in every single person. Then, during read ministration of the LHRH agonist, testosterone flares up and this causes so-called acute-on-chronic responses³⁰.

CONCLUSION

In our present study, anti-androgen was used in the medical castration group, but repeated flare-up episodes might also lead to a poor result. In this study, ADT for the treatment of advanced prostate carcinoma improved tumor progression-free survival and biochemical failure rates after 12 months for patients in the surgical castration group. When we compared Reijke⁴⁹ scores among the patients, surgical castration for patients with poor prognostic scores resulted in better disease-free survival and PSA normalization rates. The survival advantage suggests that surgical castration is beneficial in patients with poor prognosis scores, although further studies are needed to identify which patients would derive the most benefit from hormone therapy, particularly when balanced against the potential effects of long-term ADT.

Acknowledgements

The work was supported by Milad General Hospital, Tehran, Iran.

Authors' Contribution

All authors participated in designing and writing the paper.

Conflict of Interest Statement

Authors disclosed no conflicts of interests.

Funding

This project has been funded by Milad General Hospital.

"This article does not contain any studies with human participants performed by any of the authors."

"This article does not contain any studies with animals performed by any of the authors."

"This article does not contain any studies with human participants or animals performed by any of the authors."

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How to cite this article:

Dr. Sepideh Meshgi *et al* (2020) ' Evaluation of the Prognostic Level of Psa in Patients with Prostate Cancer Undergoing Orchiectomy And Drug Therapy', *International Journal of Current Medical and Pharmaceutical Research*, 06(04), pp 5072-5079.
