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# Comparative Efficacy of Goserelin vs. Leuprolide in Advanced Prostate Cancer in Patients Undergoing Androgen Deprivation Therapy

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## ABSTRACT

***Objectives*:** To determine the efficacy (achievement of castrate testosterone level at six months) of LHRH agonist therapy with different agonists, i.e., Leuprolide vs. Goserelin.

***Study Design*:** Quasi-experimental study.

***Place and Duration of Study*:** Radiation Oncology Department, Combined Military Hospital Rawalpindi Pakistan, from Jan to Oct 2020.

***Methodology***: One hundred and seventy-eight patients (n=178) having histopathologically confirmed prostate adenocarcinoma, aged 60 to 80 years, with eastern cooperative oncology group (ECOG) performance status ≤2, men with advanced prostate cancer were randomly assigned to receive different treatment, group 1(89) patients received Goserelin. 3.6mg vs group 2(89) received Leuprolide 7.5mg. The study achieved 100 % accrual in the initial 2.5 months from the start of the study. Each agent was injected intramuscularly six times every 28 days for six injections. The percentage of men whose serum testosterone concentrations fell to and remained at or below castrate levels was the primary endpoint.

***Results***: Analysis was made on 178 patients in this study. No statistically significant difference was observed between the two groups in terms of achievement of castration levels of testosterone (Leuprolide 98.9% vs. Goserline 88.7%, respectively: $p$=0.126) from baseline to 6 months. The chi-square test was applied to the outcome in both groups, and results were found to be insignificant statistically ($p$=0.126).

***Conclusion*:** In this study, no significant difference was determined between groups in attaining and maintaining castration levels of serum testosterone at six months.

**Keywords:** Advanced prostate cancer, castration, Goserelin., Leuprolide, CAB complete androgen blockade, ADT androgen deprivation therapy.

***How to Cite This Article:*** *Zeb MA, Alvi ZA, Hussain S, Wajid MIK, Riaz O, Muhammad Yousaf Khan. Comparative Efficacy of Goserelin vs. Leuprolide in Advanced Prostate Cancer in Patients Undergoing Androgen Deprivation Therapy. Pak Armed Forces Med J 2024; 74(2): 540-543. DOI: https://doi.org/10.51253/pafmj.v74i2.7522*



## INTRODUCTION

According to statistics, prostate cancer is among the top major causes of diseases and mortality in men. Each year, almost 1.6 million men are diagnosed with, and 366000 men die of prostate cancer worldwide.[1] Whenever prostate cancer is suspected, the gold standard for diagnosis is tissue biopsy, which is further helped by many other investigations to stage the disease correctly. These include magnetic resonance functional imaging and emergent biomarkers.[2] Previously, TRUS (transrectal ultrasound-guided biopsy) was standard. At the same time, efforts have been made to go for more accurate things. MRI-guided targeted biopsy has turned out to be more accurate and requires fewer overall biopsies. Moreover, it has decreased the detection of insignificant prostate cancer.[3] Nuclear medicine is evolving continuously, and the advent of a new radiopharmaceutical agent, including choline or 68 gallium, in CT scans and MRI has led to improved detection of involved lymph nodes.[4,5]

Among many treatments of prostate cancer, androgen deprivation therapy (ADT) has been the first line standard of care for patients of prostate cancer who have advanced disease and who are hormone sensitive.[6,7] ADT includes both LHRH luteinising hormone-releasing hormones agonists and antagonists. Since antagonists, e.g. Degarlix, are not readily available and are expensive, we administered LHRH agonists Leuprolide and Goserelin. to our patients. They competitively inhibit LHRH-releasing hormones and the disease since they are agonists, so they can have side effects like the flare of symptoms in the initial phase.[8]

Androgen deprivation therapy (ADT) for prostate cancer is one of the most effective treatments for advanced and metastatic prostate cancer. However, the role of ADT androgen deprivation therapy in

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*Received: 12 Dec 2021; revision received: 16 Jun 2022; accepted: 16 Jun 2022*

early-stage disease in the context of the risk-benefit ratio is poorly defined[7]. This study compared the efficacy, safety and testosterone pharmacodynamics of one-month formulations of Goserelin. and Leuprolide.

## METHODOLOGY

The quasi-experimental study was conducted after getting approval from the Ethical Review Committee (168/06/21) at the Department of Oncology, CMH, Rawalpindi Pakistan, from January to October 2020. The sample size was calculated using the WHO sample size calculator, taking the reported prevalence of prostate cancer of 5.3%.[8]

**Inclusion Criteria**: Histologically confirmed advanced prostate cancer patients (Stages C and D) T3-4NxMx, TXNI-3MX, or TXNXM1 who had bone scan within the previous three months and had a serum testosterone concentration of more than 50 nmol/L, a Karnofsky performance index of more than 40, an ECOG performance status of 2, an expected survival of more than 12 months, and no other malignancy for the next five years, were included.

**Exclusion Criteria:** Patients who had previously received hormonal therapy for prostate cancer, ECOG3/4, hypophysectomy, and adrenalectom, were excluded.

Patients were single-masked to treatment and at enrolment, and investigators and patients were unaware of the randomisation. Eligible patients were randomly assigned to receive different treatments (Figure); Group-1 (n=89) patients received Goserelin. 3.6mg, and Group-2 (n=89) received Leuprolide 7.5mg.

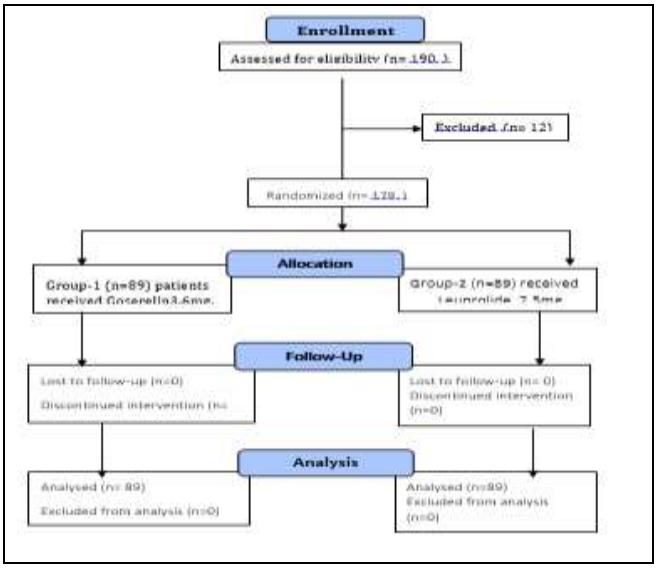


**Figure: Patient Flow Diagram (n=178)**

The study achieved 100% Accrual in an initial 2.5 months from the start of the study. The agent was injected intramuscularly every 28 days for six injections. Primary endpoints were the percentage of men whose serum testosterone concentration declined to end and were maintained at or below castrate levels < 50nml. Medical and supportive treatment necessary for the patient's welfare was given at the investigator's discretion and recorded. If analgesics were used, the patient was advised to use the same analgesics throughout the study. Treatment or procedures that affect androgenic hormones were not permitted.

Data was analysed using Statistical Package for the Social Sciences (SPSS) version 23.00 and MS Excel 2016 software. Mean±SD was calculated for continuous variables. Frequency and percentage were calculated for categorical variables. The Chi-square test was used for inferential statistics. The p-value of ≤ 0.05 was considered statistically significant.

## RESULTS

A total of 178 male patients were included in this study. The mean age of the patients was 63.05±4.26 years, ranging from 50 to 80 years. 89 patients of Group-1 received Group-1 Goserelin 3.6mg while 89 patients had Leuprolide 7. 5mg (Table-I).

**Table-I: Baseline characteristics of Study Groups (n=178)**

| Variables | Goserelin.-Group (n = 89) | Leuprolide - Group (n = 89) |
|---|---|---|
| **Age Groups** | | |
| 50-64 years | 37(42%) | 42(48%) |
| 65-80 years | 41(46%) | 45(50%) |
| **Stages** | | |
| T4NxMx | 11(12%) | 17(19%) |
| TXN1MX0 | 15(17%) | 24(27%) |
| TXMXM1 | 52(59%) | 47(52%) |

No statistically significant difference was determined between the two groups in terms of achievement of castration levels of testosterone; ($p$=0.102) (Table-II).

**Table-II: Association of Drugs with Castration/ non-castrate and ECOG PS (n=178)**

| Parameters | Drugs | | p-value |
|---|---|---|---|
| | Leuprolide - Group n=89 | Goserelin.- Group n=89 | |
| Castration<br>non-castrate | 3(3.4%)<br>86(96.6%) | 10(11.2%)<br>79(88.8) | 0.102 |
| ECOG PS<br>0 – 1<br>2 | 26(30%)<br>51(58%) | 27(31%)<br>60(77%) | 0.126 |

## DISCUSSION

Castration levels of testosterone are the primary objective of the treatment of prostate cancer. It can be achieved by a surgical method, which is subcapsular bilateral orchiectomy or medical castration using hormone therapies. Both medical and surgical castrations are equally effective, with pros and cons.[9,10] Medical castration can be CAB (complete androgen block) or ADT(Androgen deprivation therapy. In CAB (complete androgen block), we not only block LHRH (luteinising hormone-releasing hormone) from the hypothalamus and pituitary axis but also androgen receptors by adding androgen receptor blockers, including (non-steroidal) bicalutamide and flutamide. (Steroidal receptor blockers include cyproterone acetate. Surgical castration is considered to be safer in terms of long-term associated side effects.[11]

Bilateral orchiectomy causes a quick and sustained decrease in testicular androgen levels and a good quality of life. Orchiectomy has been largely replaced with medical castration because it has more patients' and physicians' acceptance. No studies have shown efficacy in terms of lowering PSA levels; there can be small differences in time duration. Only a few studies have shown the superiority of Goserelin.e over Leuprolide in terms of voiding problems.[11]

Over the past three decades, millions of patients with advanced prostate cancer have benefitted from androgen deprivation therapy. Patients and physicians have preferred it. The therapeutic effects achieved by LHRH agonists have been remarkable as treatment compared with other solid tumours as CA prostate is a hormone-driven tumour, so if we understand the androgen signalling pathway, it may help us more to understand the manipulation points in the axis for treatment.[12] Testosterone secretion starts in the hypothalamus with LHRH release in a pulsatile manner, followed by attachment to and stimulation of LHRH receptor in the anterior pituitary gland that results in the release of luteinising hormone (LH) and follicle-stimulating hormone (FSH).LH stimulates receptors on Leydig cells in the testis to induce testosterone production. Suppression of this hypothalamic-pituitary-gonadal axis is the primary mechanism by which LHRH agonists (also referred to as gonadotrophin-releasing hormone(GnRH) and antagonists reduce circulating levels of testosterone.[13]

In recent years, with the addition of novel agents, there has been an improvement in the outcome of prostate cancer. Recent additions include abiraterone acetate, apalutamide, and enzalutamide, which act on the AR receptor signalling pathway, immunotherapy (siplucil-T), docetaxel and radium-223 which is used for osseous Mets.[11]

STAMPEDE trial reported that in metastatic prostate cancer, patients who are hormone naïve once given upfront docetaxel have improved overall survival.[14] For decades, in advanced prostate cancer, the only therapy has been androgen deprivation therapy. However, with recent advancements in metastatic prostate cancer, hormone-sensitive patients have responded tremendously to more aggressive combinations, including docetaxel and abiraterone acetate. In addition to androgen deprivation therapy, Apalutamide is an androgen receptor ligand binding domain inhibitor.[15] The use of apalutamide showed increased overall survival compared to placebo and androgen deprivation therapy at 24 months.[16] Among other newer treatments, the only approved vaccine by the FDA is seleucid-T. It is used in castration-resistant prostate cancer based on the IMPACT trial. Being very expansive, it has a limited role in daily clinical practice.[17] Treatment withRadium-223 concurrently with abiraterone has helped improve overall survival as well as helpful in delaying the onset of osseous symptomatic events in CRPC with osseous metastatic disease.[18]

Nonsurgical CA prostate treatments include androgen deprivation therapy (ADT), radiation therapy (RT), ablative therapies, chemotherapy, and newer therapies such as immunotherapies. All these modalities are either used alone or in combination, depending upon the stage of the disease. ADT is used for advanced and metastatic disease. Radiation is used in place of surgery in low and intermediate disease. The ablative approach is used for low and intermediate disease or salvage treatment in progression after RT. Chemotherapy and immune-based treatments are currently used for androgen-independent diseases, although their practices are changed depending upon the results of randomised control trials. To optimise treatment effects with different modalities, the pathologist should be able to recognise the response achieved.[18]

Until the beginning of the twenty-first century, the progression of ADT for metastatic prostate cancer that was declared castration-resistant was treated with the addition of secondary hormonal manipulation, such as antiandrogens such as Bicalutamide and Nilutamide, Ketoconazole, or Corticosteroid.

Mitoxantrone was the first chemotherapy agent to be approved; now, Docetaxel, Sipleucil T, and other agents are approved and in use.[11] We used and concluded that ADT used in our setup, Goserelin. and Leuprolide, did not have any significant difference in decreasing testosterone levels and achieving medical castration.

## LIMITATION OF STUDY

Since we had to keep hard copies of patient records, things would have been easier if proper data entry desks had been provided at the institutional level.

## ACKNOWLEDGEMENT

We acknowledge the help of our colleagues at the Department of Radiation Oncology at CMH for providing us with statistical assistance and an excellent working environment.

## CONCLUSION

In this study, no significant difference was determined between groups in attaining and maintaining castration levels of serum testosterone at six months.

**Conflict of Interest:** None.

**Authors Contribution**

Following authors have made substantial contributions to the manuscript as under:

MAZ & ZAA: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

SH & MIKW: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

OR & MYK: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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