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Comparative monitoring of PSA values in prostate cancer with the use of Leuprorelin and Goserelin

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ABSTRACT

Prostate cancer is a major male malignancy driven by androgen activity. Androgen deprivation therapy (ADT) with luteinizing hormone-releasing hormone (LHRH) agonists like Leuprorelin and Goserelin is standard treatment. This retrospective study compared their effectiveness in lowering prostate specific antigen (PSA) levels. Data from 80 patients (Goserelin 3.6 mg n=21, Leuprorelin 11.25 mg n=9, Leuprorelin 22.5 mg n=50) treated between January 2014 and October 2024 at a university hospital were analyzed. PSA was measured at four time points, and clinical parameters such as Gleason score, smoking, family history, and metastasis were included. All treatments significantly reduced PSA, but differences between groups were not statistically significant (p=0.167). Although testosterone follow-up was inconsistent due to data limitations, a clear downward trend in testosterone levels was observed, indicating treatment-induced hormonal suppression. Despite variability, both agents proved effective. These findings support the continued use of either drug in ADT and highlight the need for prospective studies to explore long-term outcomes.

Keywords: prostate cancer, androgen deprivation therapy, Leuprorelin, Goserelin, PSA monitoring

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INTRODUCTION

According to GLOBOCAN, the most prevalent cancer types among males include prostate, colorectal, lung, and bronchus cancers, collectively accounting for nearly 48% of all cancer cases. Among these, prostate cancer is the most common, representing 29% of the total cases[1]. In Turkey, prostate cancer is the second most frequently diagnosed cancer in men, with an age-standardized incidence rate of 32.9 per 100,000 people, according to the Turkish Ministry of Health Cancer Statistics[2]. Prostate cancer can often be asymptomatic, meaning that many patients, particularly those with localized tumors, may succumb to the disease without ever exhibiting symptoms. Consequently, screening plays a crucial role in improving survival outcomes for prostate cancer[3]. Age, ethnicity, family history, prostate-specific antigen (PSA) levels and the free-to-total PSA ratio are among the factors that influence the likelihood of developing clinically significant prostate cancer[4].

Prostate cancer is an androgen-dependent tumor that proliferates in the presence of testosterone (T). Androgen deprivation therapy (ADT) is considered the gold standard for the initial treatment of prostate cancer[5]. Androgen suppression therapy is used as a standalone treatment for patients with localized disease. Additionally, it is administered in combination with radiotherapy for patients with locally advanced disease or those with intermediate- to high-risk localized prostate cancer[6].

Since prostate cancer is androgen-dependent, the production of PSA is also regulated by androgens[7]. PSA is a serine protease that plays a role in fertility by facilitating the breakdown of seminal fluid following ejaculation[8]. PSA production is regulated by T. As a biomarker regulated by androgen levels, PSA provides a reliable indicator for monitoring the efficacy of ADT, especially when testosterone follow-up is inconsistent[8].

ADT for castration-naive prostate cancer can be achieved through bilateral orchiectomy, the use of a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist, or a combination of an LHRH agonist with a first-generation antiandrogen. LHRH agonists and antagonists demonstrate comparable efficacy in the treatment of patients with advanced prostate cancer[9].

Leuprolide acetate is a synthetic nonapeptide LHRH agonist indicated for the palliative treatment of advanced prostate cancer. When administered continuously, it induces downregulation of pituitary gonadotropin releasing hormone (GnRH) receptors, reduces luteinizing hormone (LH) secretion, and

suppresses steroidogenesis in the testes. It is available in 1-,3-,4-, or 6-month formulations. Following the initial injection of leuprolide acetate, testosterone production is suppressed after the initial surge, and with each subsequent injection, testosterone levels remain below the castration threshold[10].

Goserelin acetate belongs to a class of drugs known as LHRH agonists. Its administration via subcutaneous injection leads to the near-complete suppression of testosterone production by the testes. Goserelin exerts a dual effect on the pituitary gland. Initially, its interaction with receptors stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The resulting surge in LH leads to a temporary increase in testosterone levels, which may contribute to tumor flare. Subsequently, Goserelin remains bound to the receptors, causing pituitary suppression and a reduction in testosterone levels to castration levels[11].

Examining the market authorization and launch dates in Turkey, Goserelin 3.6 mg has been available the longest, having been licensed since March 21, 2000. In contrast, Leuprorelin 22.5 mg, commercially known as is the most recently introduced, with market authorization granted on February 19, 2022[12].

In terms of pricing, Leuprorelin 11.25 mg and Leuprorelin 22.5 mg are similarly priced, whereas Goserelin 3.6 mg is more affordable, costing less than half of these two formulations. The difference in pricing is significantly influenced by the variations in dosage[13].

When comparing the dosing regimens specified in the monographs of active ingredients, we see that; the prescribed dosage of Leuprorelin (3-Month) is 22.5 mg, administered once every three months as a single subcutaneous injection following preparation with a specialized polymer formulation[14]. A treatment protocol may involve administering a Goserelin 3.6 mg depot injection subcutaneously into the anterior abdominal wall eight weeks before radiotherapy, followed by a Goserelin (10.8 mg) depot injection 28 days later. Alternatively, a regimen of four Goserelin 3.6 mg depot injections can be given subcutaneously into the anterior abdominal wall at 28-day intervals, with two injections administered before radiotherapy and two during the course of treatment until radiation therapy is completed[15].

When examining the side effect profiles of these drugs, the most common adverse reactions shared among them include tumor flare reaction, osteoporosis, injection site injuries, and vascular injuries. Additionally, all these medications are associated with adverse effects on the cardiovascular system. ADT may elevate cardiovascular risk in men with prostate cancer due to its

negative impact on established cardiovascular risk factors, such as increasing body weight, reducing insulin sensitivity, and contributing to dyslipidemia. Furthermore, ADT has the potential to prolong the QT/QTc interval on electrocardiogram (ECG), which may pose additional cardiovascular risks[14,15].

Numerous randomized controlled trials have compared the clinical outcomes of adjuvant hormone therapy combined with radiotherapy versus radiotherapy alone in patients with localized or locally advanced prostate cancer, as well as those with regional nodal involvement.

A previous clinical trial comparing Goserelin, Triptorelin, and Leuprorelin in patients with advanced or metastatic prostate cancer assessed testosterone suppression over a nine-month period. Among the 125 patients included, Triptorelin achieved the lowest mean testosterone levels, followed by Leuprorelin, while Goserelin showed the highest levels. Although the study demonstrated the efficacy of these agents in lowering testosterone, it did not address the impact of different dosing strategies or assess dynamic changes in PSA levels over time[16]. This study aimed to address real-world treatment effects of commonly used LHRH agonists in prostate cancer management. Our null hypothesis was that there would be no statistically significant difference in PSA reduction between patients receiving different formulations of Leuprorelin or Goserelin. Also, this study differs from previous research on similar topics by focusing not only on PSA levels but also by incorporating a broad range of clinical parameters to assess treatment response. Variables such as Gleason score, presence of metastasis, smoking history, and family history were analyzed to identify potential influences on treatment outcomes. Furthermore, by comparing two different doses of Leuprorelin (11.25 mg and 22.5 mg) with Goserelin (3.6 mg), this retrospective study offers valuable insight into dose–response relationships using real-world patient data from Turkey. The study also highlights practical issues such as irregularities in follow-up timing, which are commonly encountered in clinical settings. With these features, the research provides a novel contribution to the existing literature and distinguishes itself from previous theses.

In addition to its clinical findings, this study presents several original aspects that enhance its contribution to the current literature on LHRH agonist use in prostate cancer. While prior studies have demonstrated the efficacy of LHRH agonists in suppressing testosterone and PSA levels[9,16], few have investigated the impact of different dosages within the same formulation. By including both 11.25 mg and 22.5 mg versions of Leuprorelin, this study enables a dose-dependent analysis of PSA suppression, an area that remains underexplored in comparative endocrinologic oncology.

Moreover, PSA levels were assessed at four distinct time points, allowing for a dynamic and temporally detailed view of treatment efficacy. This contrasts with most previous studies that reported PSA outcomes at only one or two intervals[17], limiting insight into PSA kinetics over time.

The use of real-world data from a Turkish patient adds further value by reflecting prescribing trends and treatment responses in a non-trial, regional context, addressing the call for localized, population-specific research.

Finally, the integration of clinical variables—such as age, smoking status, family history, and Gleason score—enables a more nuanced and individualized analysis of treatment response, which aligns with current directions in personalized oncology[8,18]. These collective features distinguish this study and expand the existing evidence base to better inform future clinical decision-making in androgen deprivation therapy.

METHODOLOGY

This study was conducted as a retrospective study at a private university hospital in Istanbul. Ethical approval was obtained from a Non-Interventional Clinical Research Ethics Committee on September 16, 2022, with decision number 792.

Inclusion criteria required patients to be male, aged 50 or older, diagnosed with prostate cancer, and to have received three doses of Leuprorelin 11.25 mg, Leuprorelin 22.5 mg or Goserelin 3.6 mg. Patients identified as non-castration-resistant, based on the evaluation of epicrisis in their medical records, were included in the study. Patients were excluded if they had undergone hypophysectomy, adrenalectomy, or orchiectomy, had a history of alcohol dependence, corticosteroid use, or medications affecting steroid hormone metabolism, or if they were identified as having castration-resistant prostate cancer.

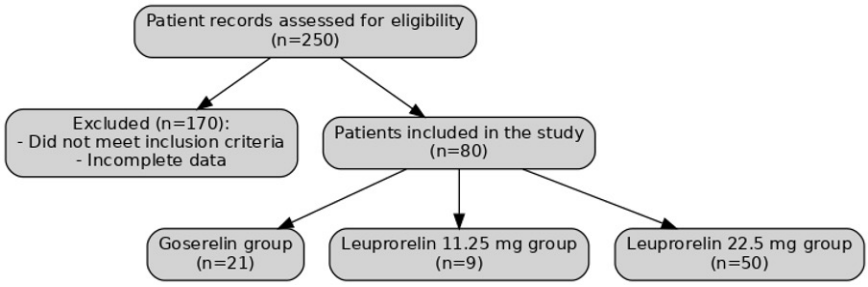

Figure 1. Patient selection flowchart

Flow diagram showing the selection of prostate cancer patients included in the study based on eligibility criteria (Figure 1).

Data were extracted from the electronic medical record system of the hospital, specifically from the Urology and Medical Oncology departments. In order to reach the sample size calculated using the G*Power program, data were collected between January 2014 to October 2024, during which patients who had been administered Leuprorelin 11.25 mg, Leuprorelin 22.5 mg, or Goserelin 3.6 mg as part of their ADT regimen were evaluated. Records were reviewed for completeness and checked for the absence of exclusion criteria before final inclusion of 80 eligible patients out of an initial 250. It should be noted that the distribution of patients across treatment groups was not uniform. This reflects real-world prescription patterns and availability of different formulations over time, which may have influenced the observed group sizes. Notably, Leuprorelin 22.5 mg was the most recently introduced agent among the options and its availability and clinical preference trends during the latter part of the data collection period may have contributed to its higher usage. These differences were acknowledged and considered during analysis. Later, the electronic medical records of patients with advanced or metastatic prostate cancer who were not castration-resistant and had been treated with Leuprorelin and Goserelin were further examined. As part of the study, various patient parameters were collected and noted, including age, smoking history, family history, presence of cardiovascular disease, Gleason score, serum PSA levels, and testosterone levels.

PSA levels were measured at four time points: PSA1 (pre-treatment), PSA2 (after first dose), PSA3 (after second dose), and PSA4 (after third dose). In addition to tracking PSA decline, this study also assessed whether treatment was administered according to guideline-recommended dosing intervals.

Although testosterone suppression to castration levels was observed, testosterone levels were not consistently monitored. In clinical practice, PSA is preferred for disease tracking due to its dynamic nature and direct association with disease activity. Literature indicates that testosterone typically falls below castration levels within 2–4 weeks of initial LHRH agonist administration and remains suppressed, thus reducing the clinical necessity for repeated measurements. Literature supports that testosterone suppression occurs rapidly and remains stable after initial dosing, reducing the necessity for repeated measurement[16,19,20].

The 2005 International Society of Urological Pathology (ISUP) revision of the Gleason scoring system defines the score as the sum of the most predominant (primary) and the second most common (secondary) tumor patterns observed

in prostate biopsy. If only one pattern is present, its grade is doubled to calculate the score. While tumor characteristics can be reported for each biopsy core individually, a global Gleason score can also be provided by considering the cumulative distribution of all patterns across positive biopsies[19].

Statistical analysis

The required sample size for this study was determined a priori using G*Power software. Based on a medium effect size (f=0.25), a significance level (α) of 0.05, and a power of 80%, a minimum of 80 participants was required to detect statistically significant differences.

For statistical analysis, normality was assessed using the Shapiro-Wilk test, and homogeneity of variance using Levene's test. When assumptions were met, one-way ANOVA (F-test) was used to compare PSA and testosterone levels among the three drug groups. If assumptions were violated, the Welch ANOVA test was applied.

For subgroup comparisons based on smoking status and family history, independent samples t-tests or Welch's t-tests were conducted depending on variance equality.

To assess changes in PSA across four time points (PSA1–PSA4), the Wilcoxon signed-rank test was used due to non-normal distribution. All analyses were conducted using SPSS, and a p-value less than 0.05 was considered statistically significant. For numerical variables with normal distribution, data are presented as Mean ± SD; for those without normal distribution, as Median (IQR); and for categorical variables, as frequencies with percentages (%).

RESULTS and DISCUSSION

A total of 250 patient records were reviewed for eligibility. After excluding patients who did not meet the inclusion criteria or had incomplete data, 80 patients were included in the final analysis (Figure 1). The patient selection process, including inclusion and exclusion criteria, is illustrated in Figure 1. These patients were subsequently categorized into three treatment groups based on the type of LHRH agonist received: Goserelin 3.6 mg (n=21), Leuprorelin 11.25 mg (n=9), and Leuprorelin 22.5 mg (n=50). The baseline demographic and clinical characteristics, as well as PSA and testosterone monitoring data across different time points, were analyzed to assess treatment outcomes.

The 80 patients included in our study were between 52 and 94 years of age (mean: 74.69 ± SD: 9.78). Their demographic and clinical data are presented in Table 1.

Table 1. Descriptive statistics of participants' demographic and clinical characteristics by drug used

Variable	Drug	Frequency	Mean	Standard Deviation
Age	Goserelin	-	76.81	9.28
	Leuprorelin 11.25 mg	-	75.33	8.72
	Leuprorelin 22.5 mg	-	73.50	10.60
Gleason Score	Goserelin	19	8.211	1.134
	Leuprorelin 11.25 mg	9	8.444	1.130
	Leuprorelin 22.5 mg	49	8.449	0.980
Variable	**Drug**	**Category**	**Frequency**	**Percentage**
Family History of Cancer	Goserelin	Yes	2	9.5
		No	19	90.5
	Leuprorelin 11.25 mg	Yes	1	11.1
		No	8	88.9
	Leuprorelin 22.5 mg	Yes	18	36.0
		No	32	64.0
Testesterone-1 Follow up	Goserelin	Yes	11	52.4
		No	10	47.6
	Leuprorelin 11.25 mg	Yes	4	44.4
		No	5	55.6
	Leuprorelin 22.5 mg	Yes	15	30.0
		No	35	70.0
Testesterone-2 Follow up	Goserelin	Yes	6	28.6
		No	15	71.4
	Leuprorelin 11.25 mg	Yes	4	44.4
		No	5	55.6
	Leuprorelin 22.5 mg	Yes	7	14.0
		No	43	86.0
Testesterone-3 Follow up	Goserelin	Yes	4	19.0
		No	17	81.0
	Leuprorelin 11.25 mg	Yes	2	22.2
		No	7	77.8
	Leuprorelin 22.5 mg	Yes	3	6.0
		No	47	94.0

Variable	Drug	Category	Frequency	Percentage
Testesterone-4 Follow up	Goserelin	Yes	2	9.5
		No	19	90.5
	Leuprorelin 11.25 mg	Yes	1	11.1
		No	8	88.9
	Leuprorelin 22.5 mg	Yes	1	2.0
		No	49	98.0
Smoking	Goserelin	Yes	8	38.1
		No	13	61.9
	Leuprorelin 11.25 mg	Yes	1	11.1
		No	8	88.9
	Leuprorelin 22.5 mg	Yes	14	28.0
		No	36	72.0
Metastasis Status	Goserelin	Yes	4	19.0
		No	17	81.0
	Leuprorelin 11.25 mg	Yes	2	22.2
		No	7	77.8
	Leuprorelin 22.5 mg	Yes	11	22.0
		No	39	78.0
Cardiovascular Disease	Goserelin	Yes	14	66.7
		No	7	33.3
	Leuprorelin 11.25 mg	Yes	4	44.4
		No	5	55.6
	Leuprorelin 22.5 mg	Yes	31	62.0
		No	19	38.0

In a study conducted by Haydaroğlu et al. (2020) at Ege University Hospital, the majority of 4,792 prostate cancer patients were in the 60-69 age group[21]. In our study, 80 male patients were evaluated, with a mean age of 74.58 years, indicating that our study group had a higher average age compared to other studies (Table 1).

The mean Gleason scores of patients using Goserelin, Leuprorelin 11.25 mg, and Leuprorelin 22.5 mg were calculated as 8.21, 8.44, and 8.45, respectively. The close similarity of these mean values and the standard deviations being approximately 1.1 across all groups suggest that the Gleason score does not appear to be a determining factor in medication selection based on the available data (Table 1).

Several studies suggest that genetic predisposition plays a key role in prostate cancer development. Hemminki & Czene (2002) reported that first-degree relatives of prostate cancer patients have a 2-3 times higher risk, increasing up to 9 times if both the father and a brother are affected[18]. Başar & Bedir (2023) similarly found that patients with a family history are at higher risk and may experience a more aggressive disease course[22]. Regarding family history in our study, 27.5% of the patients had a family history of prostate cancer, while 72.5% did not (Table 1).

Interestingly, among patients with a positive family history, Leuprorelin 22.5 mg was more frequently administered compared to other treatment groups. Specifically, 85.71% of patients with a family history received Leuprorelin 22.5 mg, whereas only 9.5% and 4.76% received Goserelin and Leuprorelin 11.25 mg, respectively (Table 1). This distribution may reflect a clinical tendency to prefer potentially more effective formulations in patients perceived to be at higher genetic risk, although this observation requires further investigation to determine whether such choices are evidence-based or coincidental.

In our study among smokers, Gleason scores were found to be lower than in non-smokers, necessitating further investigation into the impact of smoking on prostate cancer pathogenesis. While previous studies have suggested that smoking increases prostate cancer mortality[23], our data indicated that the mean Gleason-1 score was higher in non-smokers (4.218) compared to smokers (3.909).

The most commonly used medication was Leuprorelin 22.5 mg, administered to 50 patients. Goserelin was used by 21 patients, and Leuprorelin 11.25 mg by 9 patients. This distribution may reflect prescribing trends influenced by the recent introduction of Leuprorelin 22.5 mg to the market and its availability during the latter part of the data collection period.

Previous research has established the crucial role of ADT in prostate cancer management and its efficacy in suppressing testosterone levels. Mohler et al. (2019) reported that Leuprolide acetate was prescribed to approximately 90% of prostate cancer patients in the United States between 2016 and 2019, demonstrating its effectiveness in lowering serum testosterone levels[9]. Crawford et al. (2021) further stated that optimal testosterone suppression delays disease progression and improves survival, reinforcing the significance of LHRH agonists in prostate cancer treatment[24]. Our findings confirm that both drugs effectively reduce PSA levels, but no statistically significant difference was observed between them.

A noticeable decline was observed in testosterone levels over time. The mean Testosterone 1 level was 1.615 ng/dL, which decreased to 0.084 ng/dL in Testosterone 2, 0.059 ng/dL in Testosterone 3, and 0.024 ng/dL in Testosterone 4 (Table 2). These results suggest that testosterone levels decreased significantly over time and may reflect the hormonal effect of the treatment.

Table 2. Descriptive statistics of testosterone follow-up measurements

Measurement Time	Minimum (ng/dL)	Maximum (ng/dL)	Mean (ng/dL)	Standard Deviation (ng/dL)
Testosterone 1	0.031	10.011	2.063	2.796
Testosterone 2	0.025	0.442	0.080	0.111
Testosterone 3	0.025	0.231	0.059	0.072
Testosterone 4	0.019	0.025	0.024	0.003

However, it should be noted that testosterone monitoring in this study was limited and inconsistent across time points, which may have clinical implications. Suboptimal or delayed testosterone suppression can allow for ongoing androgen receptor activation, potentially resulting in biochemical progression despite apparent PSA declines. Moreover, without regular testosterone assessments, instances of incomplete hormonal castration or early treatment failure may be missed, delaying necessary therapeutic adjustments. In clinical practice, periodic monitoring of testosterone levels during androgen deprivation therapy is recommended to ensure effective castration and to detect early signs of treatment failure. As highlighted in the National Cancer Institute's Prostate Cancer Treatment guidelines, although PSA monitoring is nearly universal, there remains variability in follow-up protocols, indicating a need for robust and standardized monitoring strategies[25]. Standardized testosterone monitoring could improve early detection of incomplete castration and enable timely therapeutic escalation, ultimately impacting progression-free and overall survival outcomes. Therefore, the inconsistency in testosterone monitoring in our study highlights a real-world challenge and underscores the importance of integrating regular testosterone evaluation into routine clinical practice to optimize treatment outcomes and detect early resistance.

Unlike previous research suggesting that long-term use of androgen deprivation therapy (ADT) may contribute to bone density loss and an increased risk of cardiovascular disease[26,27], our study did not find a statistically significant association between cardiovascular comorbidity and the type of LHRH agonist used. Although 61.3% of the patients had cardiovascular comorbidities and the

use of Leuprorelin 22.5 mg appeared relatively lower among these patients, the chi-square analysis revealed no significant relationship between the presence of cardiovascular disease and medication preference (χ^2=1.342, p=0.525) (Table 3). Nevertheless, further studies with larger patient populations are needed to comprehensively assess the long-term cardiovascular and skeletal effects of ADT.

Metastasis was observed in 21.3% of patients in our study. The chi-square test (χ^2=0.083, p=0.960) showed no statistically significant association between metastasis status and the type of medication used. Among patients with metastases, the majority (88.2%) had bone involvement, while 11.8% had pelvic lymph node metastases; no cases of brain, adrenal, or other organ metastases were detected (Table 3). Most of these patients were treated with Leuprorelin 22.5 mg. These findings are consistent with previous studies indicating that prostate cancer most commonly spreads to the skeletal and lymphatic systems. Mutevelizade et al. (2024) similarly reported that bone and pelvic lymph nodes were the predominant metastatic sites as confirmed by ^{68}Ga PSMA PET/CT imaging. Rare instances of brain metastasis (0.16%) were also noted in their study. These results highlight the importance of advanced imaging techniques in the detection and staging of metastasis, as well as the need for future prospective studies to evaluate the long-term outcomes of ADT in metastatic prostate cancer[28].

Table 3. Association between drug type and presence of cardiovascular disease and metastasis

Variable	Drug	Category	Frequency	Chi-Square Test	p-value
Cardiovascular Disease	Goserelin	Yes	14	1.342	0.525
		No	7		
	Leuprorelin 11.25 mg	Yes	4		
		No	5		
	Leuprorelin 22.5 mg	Yes	31		
		No	19		
Metastasis Status	Goserelin	Yes	4	0.083	0.960
		No	17		
	Leuprorelin 11.25 mg	Yes	2		
		No	7		
	Leuprorelin 22.5 mg	Yes	11		
		No	39		

According to current clinical guidelines and product monographs, Goserelin 3.6 mg is administered subcutaneously every 28 days, while both Leuprorelin 11.25 mg and 22.5 mg are formulated as long-acting depot injections intended for administration every three months (12 weeks)[14,15,29]. The choice between these formulations is often based on patient-specific factors and availability, as both Leuprorelin doses are pharmacologically equivalent in terms of duration of action.

Despite these standardized recommendations, the analysis of drug administration intervals in our study revealed marked variability across patient groups. For Goserelin 3.6 mg, the mean interval between the first and second doses was approximately 104.6 days, far exceeding the recommended 28-day cycle. Similarly, both Leuprorelin 11.25 mg and 22.5 mg demonstrated extended and inconsistent dosing intervals, with some patients experiencing gaps as long as 586 and 677 days, respectively (Table 4). The average injection intervals between the two Leuprorelin formulations were comparable, consistent with their equal therapeutic duration. These deviations from guideline-recommended schedules likely reflect the realities of clinical practice, particularly within the context of a retrospective study design. As such, our analysis also aimed to assess whether these irregular administration patterns were associated with differences in treatment outcomes.

Table 4. Interval between drug doses

Drug and Usage Periods	Average (days)	Standard Deviation	Minimum	Maximum
Goserelin 1-2	104.571	65.712	21	286
Goserelin 2-3	87.857	22.998	21	139
Goserelin 1-3	192.429	75.550	42	385
Leuprorelin 22.5mg 1-2	100.959	42.555	52	282
Leuprorelin 22.5mg 2-3	108.180	53.030	59	364
Leuprorelin 22.5mg 1-3	209.286	85.264	142	640
Leuprorelin 11.25mg 1-2	90.444	9.289	69	104
Leuprorelin 11.25mg 2-3	147.556	168.616	37	586
Leuprorelin 11.25mg 1-3	238.000	169.168	127	677

According to current clinical guidelines, including those from the American Urological Association (AUA) and the European Society for Medical Oncology (ESMO), serial PSA monitoring is recommended at intervals of every 3 to 6 months for patients receiving androgen deprivation therapy (ADT), particularly in the context of metastatic hormone-sensitive prostate cancer[30,31]. However,

in our study, analysis of the average time intervals between successive PSA measurements showed deviations from these guidelines. The average duration between PSA1 and PSA2 was approximately 68 days (~2.2 months), which aligns well with the recommended follow-up frequency. In contrast, the intervals between PSA2–PSA3 and PSA3–PSA4 were 97 and 117 days, respectively (roughly 3.2 and 3.9 months), still within the 3–6 month window but trending toward the upper limit of recommended follow-up frequency (Figure 2). While these intervals technically fall within guideline recommendations, the progressive lengthening of time between measurements may reflect challenges in maintaining consistent follow-up in routine practice. These observations are consistent with the retrospective nature of our study, which inherently captures real-world variability in follow-up adherence. Importantly, the timing of PSA measurements remained close enough to accepted standards to allow for meaningful interpretation of treatment response.

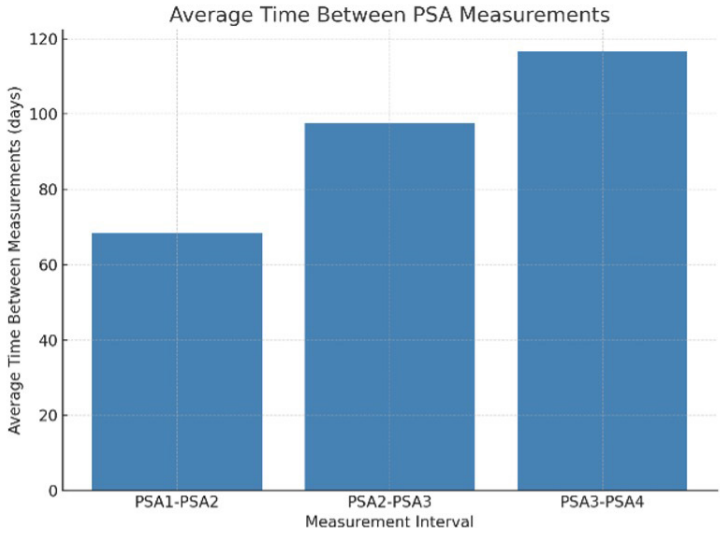

Figure 2. Average time between PSA measurements

The Gleason scores of all 80 patients were fully reported, with a mean total Gleason score of 8.390, suggesting a predominance of high Gleason scores and consequently more aggressive tumor characteristics. Correlation analysis between total Gleason score and individual PSA measurements (PSA1, PSA2, PSA3, PSA4) as well as patient age demonstrated no statistically significant relationships. All correlation coefficients were weak (r values ranging between -0.062 and 0.171) and p-values exceeded the significance threshold ($p>0.05$ for all comparisons), indicating no meaningful association between Gleason score and PSA levels or age in this study.

These findings suggest that initial Gleason score is not significantly associated with short-term biochemical response in patients undergoing androgen deprivation therapy. This observation is consistent with prior studies, including those by Shim et al. (2019) and Lawrentschuk et al. (2011), which demonstrated that although higher Gleason scores predict poorer long-term outcomes, they do not necessarily influence early PSA kinetics following LHRH agonist therapy[16,32].

Similarly, when analyzing the relationship between PSA decline rates and clinical parameters (Table 5), no significant correlations were found between Gleason score and PSA decline across different time periods. However, significant negative correlations were observed between age and PSA decline in most intervals, indicating that PSA tends to decline less with increasing age. This age-related attenuation of PSA response may be attributable to changes in androgen receptor sensitivity, tumor biology, or systemic hormonal dynamics associated with aging, thus suggesting the need for closer PSA monitoring in older patients undergoing ADT.

These results are in accordance with current European Association of Urology (EAU) guidelines, which recommend the use of LHRH agonists for the management of high-risk and advanced prostate cancer irrespective of Gleason score, emphasizing that systemic androgen suppression remains essential across varying tumor grades[33]. Our findings reinforce these recommendations by demonstrating the biochemical efficacy of LHRH agonists independent of tumor differentiation grade and support their continued use as a backbone of prostate cancer management strategies.

Table 5. Correlation between PSA decline rate and gleason score & age

	Total GLEASON		Age	
	r	p-value	r	p-value
PSA 1-2 Decline	-0.017	0.884	-0.254	0.026
PSA 1-3 Decline	0.010	0.931	-0.367	0.001
PSA 1-4 Decline	0.067	0.561	-0.395	<0.005
PSA 2-3 Decline	0.009	0.942	-0.349	0.002
PSA 2-4 Decline	0.111	0.335	-0.339	0.003
PSA 3-4 Decline	0.179	0.120	-0.237	0.038

Interestingly, analysis of PSA kinetics revealed that while most time points demonstrated a downward trend in PSA levels, certain intervals—particularly between PSA2 and PSA3, and between PSA2 and PSA4—showed a paradoxical increase in PSA values within the Goserelin group (Table 6). This is reflected by negative mean PSA decline values during these periods. Such findings may

suggest biological variability in treatment response, potential delayed onset of hormonal suppression, or patient-specific factors such as the tumor flare phenomenon, which is known to occur transiently following initial LHRH agonist administration[34,35].

Tumor flare refers to the temporary rise in testosterone levels caused by the initial overstimulation of luteinizing hormone receptors before receptor downregulation occurs, leading to transient worsening of PSA and clinical symptoms[36]. Moreover, the small sample size within each treatment subgroup, particularly in the Goserelin group may have amplified this variability, thus limiting the robustness of subgroup comparisons. These observations underscore the importance of closely monitoring PSA kinetics during early phases of androgen deprivation therapy and highlight the potential heterogeneity of treatment responses in real-world clinical populations.

Table 6. PSA decline by medication type

Variable	Drug	n	Mean (ng/ml)	Std Deviation	F Value*	p-value
PSA 1-2 decline	Goserelin	21	0.568	0.643	0.194	0.825
	Leuprorelin 11.25 mg	9	0.675	0.555		
	Leuprorelin 22.5 mg	50	0.538	0.788		
PSA 1-3 Decline	Goserelin	21	0.602	1.040	0.249	0.781
	Leuprorelin 11.25 mg	9	0.652	0.612		
	Leuprorelin 22.5 mg	50	0.439	1.616		
PSA 1-4 Decline	Goserelin	21	0.011	2.747	1.876	0.167
	Leuprorelin 11.25 mg	9	0.860	0.275		
	Leuprorelin 22.5 mg	50	0.132	3.622		
PSA 2-3 Decline	Goserelin	21	-1.226	6.677	0.506	0.609
	Leuprorelin 11.25 mg	9	0.212	0.934		
	Leuprorelin 22.5 mg	50	0.021	1.836		
PSA 2-4 Decline	Goserelin	21	-3.484	9.707	5.254	0.010
	Leuprorelin 11.25 mg	9	0.737	0.295		
	Leuprorelin 22.5 mg	50	-0.598	3.548		
PSA 3-4 Decline	Goserelin	21	-2.384	8.153	6.767	0.003
	Leuprorelin 11.25 mg	9	0.655	0.311		
	Leuprorelin 22.5 mg	50	-0.253	1.781		

*Welch Anova

No statistically significant difference was found between the groups in terms of PSA 1–2, PSA 1–3, and PSA 2–3 declines ($p>0.005$), indicating that the PSA reduction rates of the three medication groups were largely similar. Although the PSA 1–4 reduction showed a trend toward greater decline in the Leuprorelin 11.25 mg group, this difference did not reach statistical significance ($p<0.005$).

However, statistically significant differences were observed in PSA 2–4 and PSA 3–4 reductions among the groups ($p<0.005$). Pairwise comparisons using the Bonferroni test revealed that patients receiving Leuprorelin 11.25 mg demonstrated greater reductions in PSA levels between timepoints 2 and 4, and 3 and 4, compared to other groups (Table 6).

Although the PSA 1–4 reduction appeared more pronounced in the Leuprorelin 11.25 mg group compared to Goserelin and Leuprorelin 22.5 mg, this difference did not reach statistical significance. Several factors may explain this observation. First, the small sample size in the Leuprorelin 11.25 mg group ($n=9$) likely limited the statistical power to detect a significant difference despite a numerically greater decline. Small groups inherently increase the standard error and widen confidence intervals, making it harder to achieve statistical significance even when effect sizes are clinically relevant[37].

Second, baseline PSA variability among participants could have influenced percentage decline calculations. Patients in the Leuprorelin 11.25 mg group may have had differing initial disease burdens or varying biological responsiveness to androgen deprivation, leading to more favorable PSA kinetics.

Lastly, pharmacodynamic differences between lower and higher-dose formulations of Leuprorelin, including potential variations in testosterone suppression kinetics, might have contributed to the observed differences in PSA decline. A study comparing subcutaneous and intramuscular formulations of leuprolide acetate found differences in pharmacokinetics and pharmacodynamics, which could influence the degree of testosterone suppression achieved[38]. However, given the retrospective design and sample size limitations, these findings should be interpreted cautiously and warrant validation in larger prospective studies.

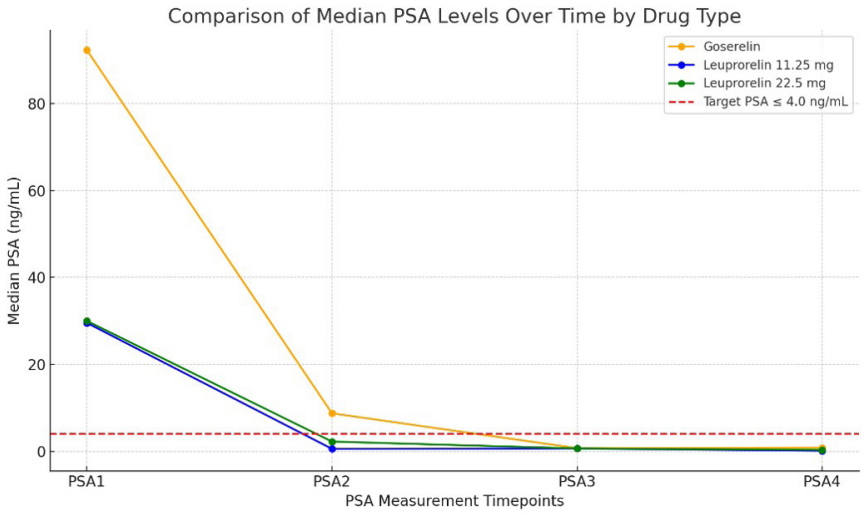

Figure 3. Comparison of median PSA levels over time by drug type

The trajectory of median PSA values across treatment timepoints provides insight into the relative effectiveness of the three LHRH agonists examined in this study. At baseline (PSA1), the median PSA values were 92.3 ng/mL for Goserelin, 29.55 ng/mL for Leuprorelin 11.25 mg, and 30 ng/mL for Leuprorelin 22.5 mg—demonstrating significant heterogeneity in initial tumor burden across treatment groups. Despite this variation, all three drugs achieved substantial reductions in PSA over time.

By the second measurement point (PSA2), PSA levels had declined dramatically in all groups, particularly in the Leuprorelin 11.25 mg group (to 0.576 ng/mL), which exhibited the fastest initial suppression. Goserelin reduced PSA to 8.75 ng/mL, while Leuprorelin 22.5 mg decreased it to 2.25 ng/mL.

From PSA2 to PSA4, Leuprorelin 11.25 mg maintained the lowest PSA levels, with PSA3 and PSA4 values of 0.652 and 0.128 ng/mL, respectively. Leuprorelin 22.5 mg also maintained effective suppression, reaching 0.3355 ng/mL at PSA4. Interestingly, Goserelin showed an unexpected rebound increase at PSA4 (0.835 ng/mL), despite having dropped to 0.727 ng/mL at PSA3.

Importantly, all three drugs successfully brought PSA levels below the clinical threshold of 4 ng/mL, indicated by the red reference line in Figure 3. However, Leuprorelin 11.25 mg appeared to sustain the most consistent and deepest suppression over time, despite being the lower-dose formulation.

Supporting these findings, overall PSA measurements throughout the study period demonstrated a clear downward trend: PSA 1 ranged from 1.15 to 4109.00 ng/mL (mean: 246.05), PSA 2 from 0.006 to 642.00 ng/mL (mean: 50.94), PSA 3 from 0.006 to 523.80 ng/mL (mean: 39.55), and PSA 4 from 0.003 to 615.00 ng/mL (mean: 30.64). The median pre-treatment PSA level was 35.70 ng/mL, exceeding the reference limit of 4 ng/mL, while the median PSA-4 level dropped to 0.406 ng/mL, confirming the effectiveness of all three treatment regimens in achieving target PSA values. While Leuprorelin 11.25 mg was associated with the most prominent and sustained PSA decline—especially within the first 12 weeks and maintained through week 24—Goserelin demonstrated a lower and more variable reduction. Leuprorelin 22.5 mg showed a moderate effect (Table 6).

These findings suggest that while all drugs are effective in achieving medical castration, Leuprorelin 11.25 mg may offer a favorable balance of dose and durable efficacy. This is particularly notable given that the higher-dose Leuprorelin 22.5 mg did not demonstrate proportionally improved outcomes, and Goserelin, despite its effectiveness, showed greater variability in late-phase control.

Supporting this, a study by Lawrentschuk et al. (2011) reported that 69.3% of patients who switched from Leuprorelin to Goserelin experienced a significant PSA reduction, whereas only 6.4% of those who switched from Goserelin to Leuprorelin showed a similar response. These findings emphasize the superior and more consistent PSA-suppressive effect of Leuprorelin, which is consistent with our study results[32].

Similarly, a study by Ishizuka et al. (2013) compared the 1-month and 3-month depot formulations of Goserelin acetate and found that both effectively reduced testosterone to castration levels. Notably, the 3-month formulation demonstrated better patient compliance. Moreover, PSA levels steadily declined during treatment, reinforcing the clinical preference for long-acting LHRH agonists. Consistent with these findings, our study confirmed that both Leuprorelin and Goserelin effectively suppressed testosterone to castration levels, maintaining this suppression for up to 24 weeks[39].

These observations align with our findings, where Leuprorelin 11.25 mg demonstrated a more sustained PSA suppression, despite the absence of statistical significance in all comparisons. These results collectively support the clinical equivalency of LHRH agonists in achieving androgen deprivation, with potential subtle pharmacodynamic differences influencing early PSA kinetics and patient response.

Based on the findings of this study, it is recommended that PSA levels should be monitored at baseline and subsequently at 3-month intervals during androgen deprivation therapy. Testosterone levels should also be measured periodically, ideally at baseline and every 6 months, to confirm maintenance of castration levels (<50 ng/dL). If PSA levels do not decline appropriately or demonstrate a rising trend after initial suppression, clinicians should consider further diagnostic workup for biochemical progression, including imaging modalities if necessary. Establishing standardized follow-up protocols based on PSA kinetics and testosterone monitoring could help optimize therapeutic outcomes and detect treatment failure earlier in clinical practice.

Considering the observed PSA decline patterns and the differences in drug pricing, cost-effectiveness becomes an important factor when selecting between treatment options. While Leuprorelin 11.25 mg demonstrated a more sustained PSA decline, particularly between timepoints 2-4 and 3-4, the absolute differences in PSA suppression were relatively modest. Given that Goserelin is substantially more affordable—costing less than half compared to Leuprorelin formulations—the minor differences in PSA kinetics may not necessarily translate into clinically significant long-term advantages that justify the higher cost. This conclusion aligns with findings from a recent cost-effectiveness analysis by Rezaee et al. (2024), which reported that Goserelin was not only the most cost-effective option among three LHRH agonists (Goserelin, Leuprolide, and Triptorelin) but also associated with the lowest total costs and a competitive effectiveness profile in terms of quality-adjusted life-years (QALYs). Their analysis, conducted using a 20-year Markov model, further reinforces the practicality of prioritizing Goserelin in clinical decision-making, particularly in resource-constrained settings[40].

These considerations align with the principles outlined in the National Comprehensive Cancer Network (NCCN) Guidelines for Prostate Cancer (Version 2.2024), which emphasize the importance of integrating both clinical efficacy and cost-effectiveness into therapeutic decision-making, particularly in healthcare systems where resource optimization is critical. Therefore, in real-world clinical practice, Goserelin may represent a more cost-effective option for certain patient populations, especially where budget constraints are present. Nonetheless, treatment decisions should be individualized, taking into account patient-specific factors such as disease aggressiveness, comorbidities, and adherence potential.

These findings underscore the need for individualized treatment approaches and suggest that LHRH antagonists may offer advantages in specific clinical

contexts, such as patients with high-volume disease or those at elevated cardiovascular risk. Incorporating antagonist-based strategies into future prospective comparative trials would further clarify their role relative to LHRH agonists in optimizing oncologic and safety outcomes in prostate cancer.

Despite the valuable insights provided by this study, several limitations should be acknowledged. One major limitation was the limited and inconsistent monitoring of testosterone levels, which hindered the ability to fully evaluate hormonal suppression throughout the treatment period and prevented robust statistical analysis in this regard. Additionally, the relatively small sample size may have limited the generalizability of the findings and reduced the statistical power of subgroup comparisons. Including a larger and more diverse patient population in future studies would enhance the reliability of intergroup analyses. Additionally, the uneven distribution of participants across treatment groups may have led to reduced statistical power in detecting potential intergroup differences, particularly for smaller subgroups such as the Leuprorelin 11.25 mg group, thereby limiting the robustness of subgroup comparisons. Moreover, considering the known adverse effects of long-term LHRH agonist therapy—such as cardiovascular complications, metabolic alterations, and bone mineral density loss—future prospective research should incorporate systematic and long-term monitoring of treatment-related adverse events to better inform clinical decision-making. These limitations are largely attributable to the retrospective design of the study, which inherently limits control over data completeness, consistency, and standardization.

In conclusion, this retrospective study demonstrates that both Leuprorelin and Goserelin are effective options for androgen deprivation therapy in prostate cancer, achieving substantial reductions in PSA and testosterone levels. Despite minor differences in PSA kinetics among formulations, no significant clinical advantage was observed favoring one agent over the others. These findings reinforce the robustness of LHRH agonists in real-world practice, irrespective of individual drug selection.

The study also highlights critical real-world challenges, such as inconsistent testosterone monitoring, which may impact early detection of treatment failure. Additionally, clinical factors such as family history, smoking status, Gleason score, and metastasis presence did not significantly influence biochemical response, underscoring the need for individualized treatment planning based on broader clinical parameters.

Future prospective studies with standardized monitoring protocols are warranted to better understand long-term outcomes, including cardiovascular health, skeletal effects, and the optimization of personalized ADT strategies in diverse patient populations.

STATEMENT OF ETHICS

Ethical approval for the study was obtained from the Non-Interventional Clinical Research Ethics Committee of Istanbul Medipol University on September 16, 2022, with the decision number E-10840098-772.02-5425.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Design and planning, EÇET, BNÇ; data collection, EÇET; data analysis, EÇET, BN; literature search and writing, ÇET; supervision, BNÇ; editing and proof reading, EÇET, BNÇ.

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