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# Retrospective Analysis of Clinical Efficacy of Luteinizing Hormone-Releasing Hormone Antagonist as Compared to Agonists with Combined Anti-Androgen Blockade (CAB) in Advanced Prostate Cancer

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## Abstract

**Purpose:** we retrospectively analyzed the clinical efficacy of the LHRH antagonist degarelix and compared it with that of the LHRH agonist's leuprolide or goserelin when used in combination with a nonsteroidal antiandrogen, bicalutamide or flutamide, for patients with advanced prostate cancer classified as stage C or D.

**Material and Method:** We examined the efficacy of degarelix, a luteinizing hormone-releasing hormone (LHRH) antagonist, and that of leuprolide and goserelin, LHRH agonists, in combination with anti-androgens for 145 advanced prostate cancers.

**Results:** When Prostate-Specific Antigen (PSA) Progression-Free Survival (PFS) was set as the primary endpoint, no significant difference was seen among the 3 agents or between the LHRH antagonist and each LHRH agonist in analysis of all patients as well as after dividing them according to stage (C/D) and J-CAPRA score (intermediate/high). Multivariate analysis showed that age <75 years old, initial PSA ≥ 200 ng/dl, and bone metastasis were risk factors affecting PSA PFS, whereas Gleason's score, lymph node metastasis, and visceral metastasis were not related.

**Conclusions:** In this retrospective analysis, we did not find a significant difference in PSA PFS between an LHRH antagonist and agonists when used with Combined Anti-androgen Blockade (CAB). Limitations include a low number of enrolled patients, lack of randomization, and retrospective nature, thus further studies with a greater number of subjects are required to confirm our results and develop an ideal protocol for hormone therapy for advanced prostate cancer.

**Keywords: Combined androgen blockade; Metastatic prostate cancer; Luteinizing hormone-releasing hormone; Antagonist; Agonist**

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## Introduction

Since Huggins and Hodges [1] reported the efficacy of castration and estrogen treatment, primary Androgen Deprivation Therapy (ADT) has become the gold-standard therapy for metastatic prostate cancer. Although medical castration using the luteinizing hormone-releasing hormone (LHRH) agonists leuprolide and goserelin has been utilized as ADT for more than 2 decades, a new type of hormonal therapy that employs the LHRH antagonist degarelix has recently appeared and been shown to provide fast testosterone suppression without surge or clinical flare-up generally associated with LHRH agonist therapy [2,3]. Patients with localized, locally advanced, or metastatic

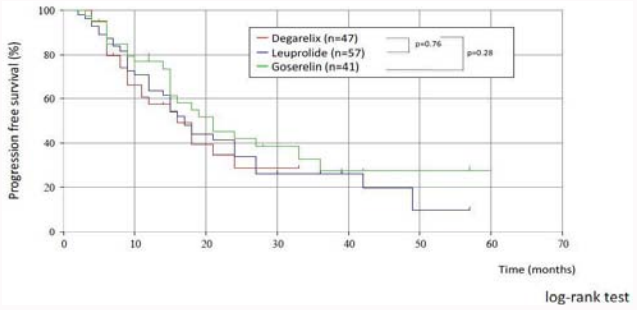


**Figure 1:** Probability of PSA PFS survival for all patients. There was no significant difference between the groups in log-rank test findings (degarelix *vs.* leuprolide; p=0.76, degarelix *vs.* goserelin; p=0.28). Red bar: degarelix group; blue bar: leuprolide group; green bar: goserelin group.

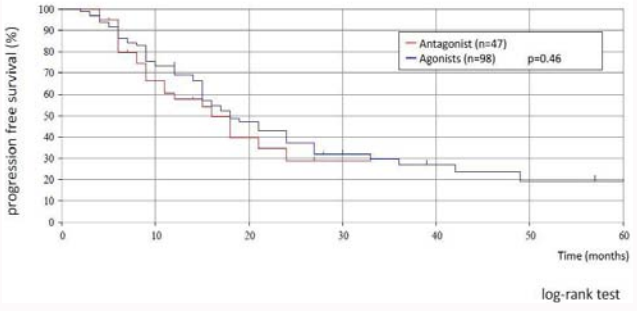


**Figure 2:** Probability of PSA PFS in all patients. There was no significant difference between the groups in log-rank test findings (antagonist *vs.* agonists; p=0.464). Red bar: antagonist group; blue bar: agonist group.

prostate cancer administered degarelix as monotherapy without anti-androgens have been reported to show higher Prostate-Specific Antigen (PSA) Progression-Free Survival (PFS) as well as overall survival (OS) [4,5]. Notably, patients in those studies with PSA >20 ng/ml who received degarelix had a significantly longer time to PSA recurrence as compared to those who received either leuprolide or goserelin.

Thus, since degarelix has been shown to be superior to LHRH agonists as monotherapy in terms of PFS and OS for patients in various stages, including early to moderately advanced prostate cancer; it may have an advantage over LHRH agonists for treating highly advanced cancer. In Japan, Combined Anti-androgen Blockade (CAB) is used in approximately 70% of the cases of primary hormone therapy for prostate cancer [6]. In patients with a very high Japan Cancer of the Prostate Risk Assessment (J-CAPRA) score, it has been reported that CAB results in significantly better OS and Cancer Specific Survival (CSS) as compared to those who received another therapy [7-9]. Thus, it is questionable whether degarelix would demonstrate superior performance as compared to LHRH agonists when used as CAB with nonsteroidal anti-androgens, which are given to prevent flare-up associated with the start of LHRH agonist therapy [10], as well as block the influence of androgens from all sources including adrenal androgens [11].

In the present study, we retrospectively analyzed the clinical efficacy of the LHRH antagonist degarelix and compared it with that of the LHRH agonist's leuprolide or goserelin when used in combination with a nonsteroidal anti-androgen, bicalutamide or flutamide, for patients with advanced prostate cancer classified as stage C or D.

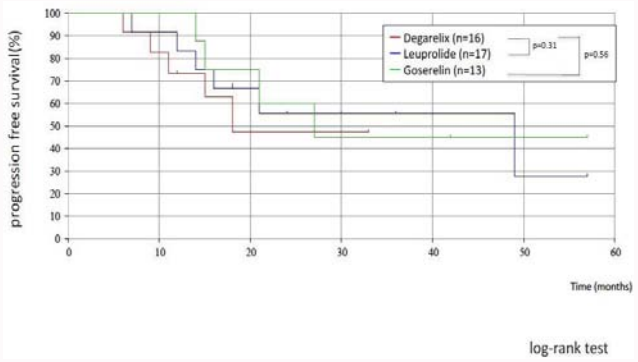


**Figure 3:** Probability of PSA PFS in patients with intermediate J-CAPRA score. There was no significant difference between the groups in log-rank test findings (degarelix *vs.* leuprolide; p=0.31, degarelix *vs.* goserelin; p=0.56). Red bar: degarelix group; blue bar: leuprolide group; green bar: goserelin group.

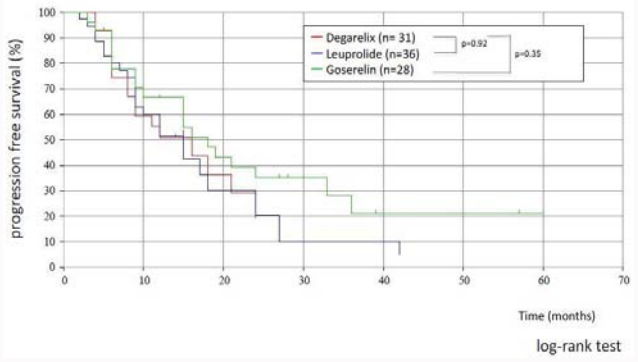


**Figure 4:** Probability of PSA PFS in patients with high J-CAPRA score. There was no significant difference between the groups in log-rank test findings (degarelix *vs.* leuprolide; p=0.92, degarelix *vs.* goserelin; p=0.35). Red bar: degarelix group; blue bar: leuprolide group; green bar: goserelin group.

## Patients and Methods

Medical records at 6 institutions were reviewed to find patients with stage C or D prostate cancer treated with CAB with nonsteroidal anti-androgens for prostate cancer during the period from January 2010 to December 2015, with 176 identified who were also given an LHRH antagonist or agonist (degarelix 50, leuprolide 77, goserelin 49). Of those, 31 were excluded because of unknown Gleason's Score (GS) or TNM staging, and 2 because of being lost to follow up, thus finally 145 patients (degarelix 47, leuprolide 57, goserelin 41) were enrolled for this retrospective analysis. Patient background information is shown in Table 1. There were significant differences found for GS, e.g., the leuprolide group included patients with a lower GS than the patients who received degarelix or goserelin, as shown in Newman-Keuls and chi-square test findings. No significant differences were found for the other factors, including initial PSA value, metastatic lesions, C/D stage, and J-CAPRA score at diagnosis.

The primary endpoint was PSA-PFS rate and PSA recurrence was defined as an increase in PSA value by >25% relative to the baseline or increase in absolute value ≥ 2.0 ng/ml [12]. The PSA- PFS was examined using the Kaplan-Meier method, and compared between patients administered degarelix and leuprolide or goserelin by log-rank test. We developed Cox proportional hazards models to estimate the Hazard ratio [HR] and its 95% Confidence Intervals [95% CIs] between degarelix, leuprolide, and goserelin adjusted for age (<75 *vs.*

**Table 1:** Patient background information.

| | | Degarelix (n=47) | Leuprolide (n=57) | Goserelin (n=41) | |
|---|---|---|---|---|---|
| Age | | 72 ± 8.65 (51-90) | 77 ± 7.56 (58-94) | 76.5 ± 8.16 (54-89) | p=0.56† |
| Initial PSA (ng/ml ) | | 207.8 ± 2065.2 (10.8-9943) | 180.7 ± 941.0 (5.511-5200) | 175.4 ± 2544.2 (10.1-17,115) | p=0.59† |
| Gleason's score | ≤ 7 | 7 | 21 | 8 | p=0.02‡ |
| | ≥ 8 | 40 | 36 | 33 | |
| Metastatic lesion | Bone | 30 | 35 | 27 | p=0.31‡ |
| | LN | 27 | 13 | 18 | |
| | Lung | 3 | 5 | 3 | |
| | Liver | 1 | 0 | 0 | |
| Clinical stage | C | 10 | 12 | 5 | p=0.45‡ |
| | D | 37 | 45 | 36 | |
| J-CAPRA | Low | 0 | 3 | 0 | p=0.30‡ |
| | Intermediate | 16 | 17 | 13 | |
| | High | 31 | 37 | 28 | |

Data are presented as mean ± SD or N (%). † Newman-Keuls test; ‡ Chi-square test.

≥ 75 years), PSA (<200 *vs.* ≥ 200 ng/ml), Gleason's score ( ≤ 7 *vs.* ≥ 8), LN metastasis (negative *vs.* positive), Bone metastasis (negative *vs.* positive), Visceral metastasis (negative *vs.* positive). We divided the patients into subgroups based on C/D stage and intermediate/high J-CAPRA score.

We used the StatMate V® (ATMS Co. Ltd), and two-tailed p-values less than 0.05 were considered statistically significant.

The present study was approved by the ethics committee of each participating institute (Hyogo College of Medicine #2415).

## Results

When overall PSA PFS was compared among the 3 agents, there was no significant difference regarding 50% PFS in the groups administered degarelix, leuprolide, or goserelin (16, 17, 21 months, respectively) (Figure 1). Similarly, no significant difference was found between degarelix and either of the LHRH agonists (50% PFS; 16 *vs.* 18 months) (Figure 2). Univariate analysis as well as multivariate analysis revealed that risk factors affecting PFS were age <75 year-old, initial PSA ≥ 200 ng/ml, and bone metastasis were related, whereas GS, Lymph Node (LN) metastasis, and visceral metastasis were not shown to be related (Table 2A and 2B).

In subgroups divided based on stage (C or D), when PSA PFS was compared among the 3 agents or between degarelix and both LHRH agonists, there was no significant difference found. As for risk factors affecting PFS, older age and higher initial PSA level were shown in the stage D subgroup, while no risk factors were found in the in stage C subgroup, probably because of the low number of patients in the latter (data not shown).

We also divided into subgroups based on intermediate J-CAPRA score. When PSA PFS was compared among the 3 agents as well as between degarelix and both LHRH agonists, no significant differences were found (Figure 3) and no risk factor was detected by univariate analysis (Table 3).

Furthermore, subgroups were divided based on high J-CAPRA score, and then PSA PFS was compared among the 3 agents as well as between degarelix and both LHRH agonists. No significant difference found regarding 50% PFS in the groups administered degarelix, leuprolide, or goserelin (16, 15, 18 months, respectively)

**Table 2A:** Univariate analysis of PSA PFS in all patients.

| | Hazard ratio (95% CI) | p value |
|---|---|---|
| Degarelix *vs.* Leuprolide | 0.97 (0.57-1.67) | 0.93 |
| Degarelix *vs.* Goserelin | 0.74 (0.41-1.36) | 0.34 |
| Antagonist *vs.* Agonists | 0.87 (0.49-1.54) | 0.65 |
| Age (<75 *vs.* ≥ 75 years) | 0.63 (0.40-0.97) | 0.039 |
| PSA (<200 *vs.* ≥ 200 ng/ml) | 2.24 (1.43-3.50) | <0.001 |
| Gleason's score (≤ 7 *vs.* ≥ 8) | 1.10 (0.62-1.95) | 0.72 |
| LN metastasis (negative *vs.* positive) | 1.26 (0.81-1.97) | 0.29 |
| Bone metastasis (negative *vs.* positive) | 2.80 (1.61-4.85) | <0.001 |
| Visceral metastasis (negative *vs.* positive) | 0.94 (0.43-2.06) | 0.89 |

Cox proportional hazards model

**Table 2B:** Multivariate analysis of PSA PFS in all patients.

| | Hazard ratio (95% CI) | p value |
|---|---|---|
| Age (<75 *vs.* ≥ 75 years) | 0.56 (0.36-0.88) | 0.012 |
| PSA (<200 *vs.* ≥ 200 ng/ml) | 2.03 (1.27-3.23) | 0.002 |
| Bone metastasis (negative *vs.* positive) | 2.41 (1.37-4.24) | 0.002 |

Cox proportional hazards model

(Figure 4), while similar risk factors including higher initial PSA level by univariate analysis (Table 4A), and younger age and higher initial PSA level by multivariate analysis were demonstrated (Table 4B).

## Discussion and Conclusion

Administration of an LHRH agonist causes a transient increase in testosterone by overstimulating LHRH receptors, eventually leading to suppression of LH release through desensitization of the pituitary gland, a mechanism that results in an initial clinical flare-up that stimulates tumor growth and worsens clinical symptoms in patients with advanced prostate cancer [13]. Continuous repeated treatments with an LHRH agonist can also cause testosterone micro-surges, which result in inconsistent testosterone levels within the castration range [14]. This is considered to be the main reason why use of an LHRH antagonist has a clinical advantage as compared with agonists, because the former when used as monotherapy immediately blocks LHRH receptors, resulting in rapid testosterone suppression without surge, flare-up, or micro-surges [2,3].

**Table 3:** Univariate analysis of PSA PFS in patients with intermediate J-CAPRA score.

| | Hazard ratio (95% CI) | p value |
|---|---|---|
| Degarelix *vs.* Leuprolide | 1.04 (0.30-3.52) | 0.94 |
| Degarelix *vs.* Goserelin | 0.80 (0.19-3.23) | 0.75 |
| Antagonist *vs.* Agonist | 0.94 (0.29-2.97) | 0.92 |
| Age (<75 *vs.* ≥ 75 years) | 0.74 (0.27-1.99) | 0.55 |
| PSA (<200 *vs.* ≥ 200 ng/ml) | 1.05 (0.32-3.40) | 0.92 |
| Gleason's score (≤ 7 *vs.* ≥ 8) | 0.68 (0.22-2.04) | 0.49 |
| LN metastasis (negative *vs.* positive) | 0.48 (0.11-2.14) | 0.34 |
| Bone metastasis (negative *vs.* positive) | 2.30 (0.85-6.23) | 0.1 |

Cox proportional hazards model

**Table 4A:** Univariate analysis of PSA PFS in patients with high J-CAPRA score.

| | Hazard ratio (95% CI) | p value |
|---|---|---|
| Degarelix *vs.* Leuprolide | 1.04 (0.57-1.91) | 0.87 |
| Degarelix *vs.* Goserelin | 0.68 (0.35-1.35) | 0.27 |
| Antagonist *vs.* Agonists | 0.87 (0.49-1.54) | 0.87 |
| Age (<75 *vs.* ≥ 75 years) | 0.63 (0.38-1.04) | 0.07 |
| PSA (<200 *vs.* ≥ 200 ng/ml) | 1.94 (1.14-3.30) | 0.013 |
| Gleason's score (≤ 7 *vs.* ≥ 8) | 0.79 (0.38-1.61) | 0.52 |
| LN metastasis (negative *vs.* positive) | 1.00 (0.61-1.66) | 0.97 |
| Bone metastasis (negative *vs.* positive) | 1.89 (0.93-3.82) | 0.07 |
| Visceral metastasis (negative *vs.* positive) | 0.69 (0.31-1.52) | 0.36 |

Cox proportional hazards model

**Table 4B:** Multivariate analysis of PSA PFS in patients with high J-CAPRA score.

| | Hazard ratio (95% CI) | p value |
|---|---|---|
| Age (<75 *vs.* ≥ 75 years) | 0.51 (0.31-0.86) | 0.01 |
| PSA (<200 *vs.* ≥ 200 ng/ml) | 2.16 (1.22-3.84) | 0.008 |
| Bone metastasis (negative *vs.* positive) | 1.55 (0.75-3.22) | 0.23 |

Cox proportional hazards model

The principal aim of CAB is to prevent flare-up at the start of LHRH agonist therapy [10] as well as neutralize adrenal androgens [11]. CAB is popular in Japan, as it has been demonstrated to show better OS and CSS as compared to monotherapy without reducing patient tolerability, especially in those with a very high J-CAPRA score [7-9]. In contrast, a systematic review suggested that CAB should not be routinely given to patients with metastatic prostate cancer beyond the purpose of blocking a testosterone flare-up, because of the small survival benefit with added toxicity and concomitant decline in quality of life [15]. As a result, monotherapy with an LHRH agonist or antagonist is popular in Western countries.

In the present study, we retrospectively assessed the efficacy of an LHRH antagonist, degarelix, and compared it with that of 2 LHRH agonists, leuprolide and goserelin, when used in combination with anti-androgens for treatment of Japanese patients with advanced prostate cancer (stage C/D). When PSA PFS was set as the primary endpoint, the results showed no significant difference among the 3 agents or between degarelix and the LHRH agonists, including overall analysis as well as subgroup analysis after dividing based on stage and J-CAPRA score. Our findings indicate that use of either an antagonist or agonist will have the same effect on PSA PFS when given together with CAB as primary hormone therapy for advanced cancer. On the other hand, younger age (<75 years) was shown to be a risk factor for unfavorable PFS by multivariate analysis, suggesting that PFS in younger patients given degarelix may be adversely affected. Although the lower GS value in the present leuprolide group should be carefully considered, PFS was not significantly different in overall findings or after dividing into subgroups based on J- CAPRA score.

In conclusion, in the present retrospective study we did not find a significant difference in PSA PFS between an LHRH antagonist and 2 different agonists when used in combination with anti-androgens for advanced prostate cancer. However, our findings are limited by the low number of patients enrolled, lack of randomization, and retrospective nature. Additional studies with a greater number of subjects are needed to confirm these results and for development of an ideal hormone therapy protocol for advanced prostate cancer.

## Acknowledgment

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This retrospective study was approved by the formal ethics committee; the principles of the Helsinki Declaration were followed.

## Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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