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Original Article

Predictive factor of androgen deprivation therapy for patients with advanced stage prostate cancer

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ABSTRACT

Background: The purpose of this study was to identify the predictive factors for the efficacy of androgen deprivation therapy (ADT) in men with hormone-sensitive prostate cancer (PC) with or without distant metastasis.

Methods: A retrospective review of PC patients was conducted of the medical records. We enrolled 246 patients who received primary ADT. PC patients treated with ADT for presumed nonlocalized PC were evaluated on the efficacy of ADT using prostate-specific antigen (PSA) time to progression (TTP) and compared factors associated with TTP in patients with distant metastasis and patients without distant metastasis.

Results: A total of 246 patients were treated primarily with ADT. The median follow-up period was 20.2 months. One hundred and ninety-one patients had metastatic disease. The median TTP on ADT for the distant metastasis group was 14.8 months versus 60.1 months in the without distant metastasis group ($P < 0.0001$). In the univariate analysis only, PSA nadir after ADT was associated with longer TTP (hazard ratio, 10.69; 95% confidence interval, 5.56–20.57). In the multivariate analysis, high grade tumor and PSA nadir were independent factors associated with a shorter TTP.

Conclusion: In this study of hormone-sensitive PC patients treated with ADT for nonlocalized PC, high grade tumor and PSA nadir were predicting factors of this treatment.

1. Introduction

Prostate cancer (PC) is the most common cancer diagnosed in genitourinary cancer. The incidence in Thailand is 7.2/100,000 of population and the mortality is 3.7/100,000.[1] In Thailand, patients usually present with advanced stage PC when compared with the USA and Europe.[2] The treatment of choice for patients with advanced stage PC is androgen deprivation therapy (ADT). However, ADT is not curative in patients with locally advanced or metastatic disease.[3–7] Despite the initial response to ADT, most patients will experience disease progression and the development of castration-resistant PC (CRPC).[8,9] The majority of previous studies reported that a longer time to the prostate-specific antigen (PSA) nadir was associated with better survival.[10–12] The predictive factors for the efficacy of ADT in men with hormone-sensitive PC (HSPC) are still unknown. It is important to investigate the prognostic markers that can reflect survival in advanced stage PC. The results may affect the treatment strategy, especially for patients with disease progression.

We queried a longitudinal database of patients treated at Songklanagarind Hospital, Songkhla, Thailand to describe the outcome of ADT use in men with HSPC with or without distant metastases at the time of ADT initiation. Our interest was time to progression (TTP) and factors associated with TTP.

2. Materials and methods

Ethical approval for the study was obtained from the Institutional Review Board of Songklanagarind Hospital. The medical records of all PC patients treated primarily with ADT, either in the form of gonadotropin-releasing hormone agonists or bilateral orchiectomy in Songklanagarind Hospital from 2008 to 2015 were reviewed. We also enrolled patients with locally advanced

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PC and metastatic PC which were not suitable for local treatment. The nadir PSA level was defined as the lowest PSA level after ADT. Disease progression was defined as a 25% increase from the baseline value along with an increase in the absolute value of 2 ng/mL after 12 weeks of treatment.[13] The urologist in charge appointed every patient for clinical examination and serum PSA level every 3 months. A bone scan was used to detect further bone metastases for patients who developed bone pain during ADT treatment. In the case of bone scan progression together with rising PSA, these patients were diagnosed with metastatic RCPC (mCRPC) and went through treatment for mCRPC.

Of 258 patients identified, 246 met all entry criteria. All data were obtained by reviewing the patient histories, imaging studies, operative records, and as discharge summaries. Patients and disease characteristics including age, Gleason score, initial PSA level, bone scan imaging, time of follow-up, mode of ADT, treatment modality upon disease progression, baseline PSA, PSA nadir, and TTP were reviewed.

2.1. Statistical analysis

The statistical analysis was carried out using the R software 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and $P < 0.05$ was considered to be statistically significant. The overall survival was estimated by the Kaplan–Meier method. The log rank test was used to assess differences between the groups. The Cox proportional hazards regression model was performed to analyze the independent predictors of TTP. Only the variables that were found to be significant in the univariate analyses ($P < 0.05$) were entered into the multivariate analysis to determine the most significant factors to predict the disease outcome.

3. Results

3.1. Patient characteristics and PSA profile

A total of 246 patients were treated primarily with ADT from January 2008 to May 2015. The characteristics of the patients are shown in Table 1. Overall, 191 patients (77.6%) had metastatic disease at the initiation of ADT treatment. The mean age was 72.7 (± 9) years. The ADT treatment was bilateral orchiectomy in 48.8% of the patients. The median follow-up time was 20 months (range, 11–35 months).

Most patients responded to ADT. The median nadir PSA level was 2.55 ng/mL (range, 0–500 ng/mL). Forty patients (16.3%) reached a nadir PSA < 0.2 ng/mL and 60.6% of patients reached PSA < 4 ng/mL. Most of the PC patients had high grade tumor (54.9%). Only 19 patients had low grade tumor.

The overall TTP was 19 months. In the locally advanced PC group, the TTP was 60.1 months. By contrast, TTP in the metastatic group was 14.8 months. Patients who could not reach a PSA < 4 ng/mL had a TTP of 11.5 months. Table 2 summarizes the association between TTP and disease characteristics. The mean PSA at diagnosis was 354 ng/mL (range, 2–3250 ng/mL). An initial PSA > 50 ng/mL had a TTP of 18.9 months. The TTP in patients with an initial PSA ≤ 50 ng/mL was 25.1 months. Most patients had initial PSA > 50 ng/mL, 89% in the metastatic group and 80% in the locally advanced group. There were no differences in the TTP between the gonadotropin-releasing hormone agonist and surgical castration groups (Table 2).

3.2. Univariate and multivariate analysis of predictor for TTP

With a median follow-up time of 20 months, several factors were identified that predicted TTP after initial ADT treatment on univariate and multivariate analysis (Table 3). The nadir PSA of > 4 ng/mL in high grade tumor was significantly associated with a short TTP (Fig. 1). By contrast, a PSA at diagnosis of ≤ 50 ng/mL was significantly associated with a long TTP.

Table 1
Demographic and clinical characteristics by the primary ADT.

	Overall	Locally advanced	Metastatic disease	*P*
Mean age (yr)	72.7	74.7	72.1	0.059
Gleason score				0.774
≤ 6	19	4	15	
7	92	23	69	
8–10	135	28	107	
Median base line PSA (ng/mL)	297	115	476	< 0.001
Follow-up (mo)	20.2	35.4	18.1	< 0.001
Mode of ADT				0.011
GnRH agonist	126	37	89	
Bilateral orchiectomy	120	18	102	
Median nadir PSA	2.5	0.5	3.6	< 0.001
Median TTP (mo)	19	60.1	14.8	< 0.001

ADT, androgen deprivation therapy; PSA, prostate-specific antigen; TTP, time to progression.

Table 2
Association between time to progression (TTP) and disease characteristics.

	Overall	Locally advanced	Metastatic disease
Gleason score			
≤ 6	37.5	47.8	37.5
7	27.9	69.9	18.1
8–10	14.8	52.7	12.5
Initial PSA			
≤ 50	25.1	47.8	22.1
> 50	18.9	60.1	14.8
PSA nadir			
≤ 0.2	N/A	N/A	43.5
0.2–4	23.7	52.7	19.0
> 4	11.5	38.5	10.4
Mode of ADT			
Medical ADT	18.9	69.6	14.3
Surgical ADT	19.8	53.7	15.9

ADT, androgen deprivation therapy; PSA, prostate-specific antigen.

Table 3
Hazard ratio estimates and confidence intervals from proportional hazards modeling of time to progression (TTP).

Overall				
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Gleason score				
≤ 6	1	0.013	1	0.003
7	1.25 (0.61–2.54)		1.84 (0.86–3.91)	
8–10	1.92 (0.97–3.8)		2.72 (1.31–5.64)	
Mode of ADT		0.428		0.636
Orchiectomy	1		1	
GnRH agonist	0.88 (0.64–1.2)		1.08 (0.78–1.49)	
Initial PSA		0.635		0.059
≤ 50	1		1	
> 50	1.13 (0.69–1.84)		0.58 (0.33–0.99)	
PSA nadir				
≤ 0.2	1	< 0.001	1	< 0.001
0.2–4	3.81 (1.98–7.31)		4.01(2.08–7.73)	
> 4	10.69 (5.56–20.57)		12.19(6.25–23.77)	

ADT, androgen deprivation therapy; CI, confidence interval; GnRH, gonadotropin-releasing hormone agonist; HR, hazard ratio; PSA, prostate-specific antigen.

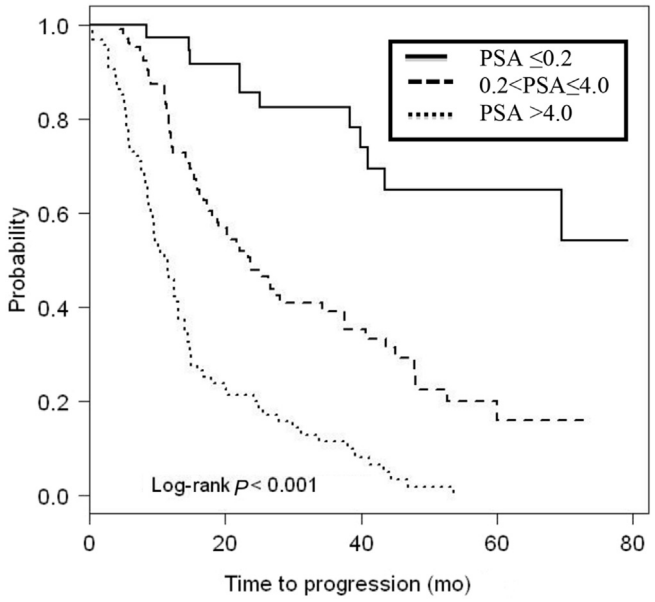

Fig. 1. Time to progression (TTP) according to the nadir prostate-specific antigen (PSA) and the time to PSA nadir.

4. Discussion

A rising PSA after the nadir value under ADT represents the first objective sign of CRPC. PSA recurrence usually predates clinical progression of metastatic prostatic cancer after ADT.[14] Once CRPC comes into existence, patients will die within 3 years.[15] Recent studies confirmed the importance in TTP in overall survival and progression free survival.[16–18] In this retrospective cohort of 246 patients treated with ADT, prognostic factors for PC were evaluated for age, initial PSA, Gleason score, state of disease, and PSA nadir after ADT. We sought to identify risk factors for the prognosis in a series of patients with advanced PC who were treated with ADT. Our findings indicated that the initial PSA, high grade tumor, and PSA nadir after ADT (< 4 ng/mL) were the prognostic factors for TTP.

In a subgroup analysis, the metastatic disease group with high grade tumor was associated with a shorter TTP (hazard ratio, 2.49; 95% confidence interval, 1.15–5.41) but we did not find this association in the locally advanced group. These results correspond with the study from Ross et al[8] which reported that in the locally advanced group the PSA nadir was the only independent factor with a shorter TTP. In contrast, Varenhorst et al[19] reported the level of pretreatment PSA or the Gleason score at diagnosis could not predict patients likely to be unresponsive to ADT. They mentioned that patients with a low Eastern Cooperative Oncology Group performance status, analgesic consumption, high Soloway score, and a low hemoglobin level were found to be predictive of early ADT failure.[19]

Only 11 patients in the locally advanced group had initial PSA ≤ 50 ng/mL. Four of them had Gleason 9 and one patient had Gleason 10. This may be because of shorter TTP in the locally advanced group. The TTP in the metastatic group in this cohort was 14.8 months. This may represent the aggressiveness of the tumors in our population. In order to lengthen the TTP, we decided to change our policy of treatment. The study from the Chaarted Trial which shared the benefit of early chemotherapy in the group of patients who had high volume metastasis shared some of the demographic characteristics with our patient population.[20] In Thailand, we currently have no policy to screen for PC. Therefore, many cases present with advanced PC which is not amenable to definite local treatment. ADT is the treatment of choice in such patients. The national health policy states that patients with advanced disease must do a bilateral orchiectomy for ADT. In our study, nearly 50% of the patients received bilateral orchiectomy as their primary ADT approach. Despite the recommended treatments of radiotherapy plus ADT in locally advanced PC, most patients in this hospital preferred ADT alone due to their elderly age and the side effects of radiotherapy. In the past few years, we have changed the treatment to radical prostatectomy. Although the optimal treatment approach for these patients remains uncertain, there is a tendency for patients who are healthy, younger, and have low-volume tumors to receive radical surgical treatment.[21,22] We hope that the concept of chemohormonal treatment for HSPC will be the next step to lengthen the TTP in our hospital.

There are several limitations in our study. It is a retrospective design and dependent on data that may affect the accuracy of the results. There was no standard follow-up or imaging protocol. The serum testosterone was not routinely checked or monitored in our cohort. We believe these data could be useful to decide on the best treatment strategy to predict patients who are likely to develop early progression to CRPC.

In conclusion, we believe that a longer TTP is associated with a better prognosis. Patients with a shorter TTP may potentially have more aggressive disease and second-line treatment may be considered early on. The TTP was dependent on the initial PSA level and PSA nadir after ADT. This data can be used to advise patients on the potential efficacy of ADT.

Conflicts of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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