Original Article

Progression time of de novo metastases in relation to castration resistant prostate cancer at a tertiary care hospital in Southern Thailand

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Metastasis prostate cancer, androgen deprivation therapy, orchiectomy, castration-resistant prostate cancer, high volume metastatic prostate cancer

Abstract

Objective: Androgen deprivation therapy (ADT) is often the treatment of choice in metastatic prostate cancer patients. However, there is currently an insufficiency of biomarker-related data that can be used in order to predict how the disease would respond to ADT. In this study we evaluated the clinical response to ADT, including factors which are affecting the progression of the disease into castration-resistant prostate cancer (CRPC) in patients with de novo metastatic prostate cancer.

Materials and Methods: This retrospective study incorporated patients with metastatic prostate cancer who received ADT at our center from January 2008 to December 2019. Baseline characteristics, mode of ADT, prostate-specific antigen (PSA), blood chemistry, Gleason score (GS) grade group, location, and the number of metastases were analyzed. The risk factors affecting the progression of the disease were identified.

Results: Data from 125 patients were included in the study. One hundred patients (80%) were classified as suffering from high volume metastatic prostate cancer and six patients (6%) with visceral metastasis. Baseline PSA in high volume and low volume metastatic prostate cancer were defined as 500 ng/ml and 215.1 ng/ml respectively. Eighty-one patients (64.8%) received a gonadotrophin-releasing hormone (GnRH) agonist while 42 patients (33.6%) underwent bilateral orchiectomy. Time to CRPC in high and low volume metastasis was 12 months and 23 months respectively. Patients with Alkaline Phosphatase (ALP) ≥350 U/L had 8.5 months to CRPC while patients with ALP <350 U/L had 15 months. High GS grade group (3-5), short time to PSA nadir (<6 months), PSA nadir level (≥ 2 ng/ml), and serum ALP ≥350 U/L were independent factors associated with shorter time to CRPC.

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Conclusion: The clinical management of metastatic prostate cancer is challenging; the main aims of treatment are to prolong overall survival whilst maintaining quality of life. Patients with aggressive tumors, high volume metastasis, short time to nadir (TTN), high PSA nadir level, and high ALP level were independent factors associated with shorter time to CRPC.

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Introduction

Prostate cancer is the most common urologic cancer. The estimated incidence of prostate cancer in Thailand is 7.2 per 100,000 population and the mortality rate is 3.7 per 100 000 with a 5-year prevalence of 14.9%.[1] The most common organ metastasis is to the bones.[2] Patients with de novo metastatic disease at presentation have a poorer prognosis compared with patients who relapse after local therapy. The main treatment for patients with de novo metastatic prostate cancer is androgen deprivation therapy (ADT). Treatment aims to inhibit and delay disease progression into Castration-resistant Prostate Cancer (CRPC); a condition that is resistant to hormone inhibition therapy and is associated with poor prognosis and survival rates.[3] Currently, upfront treatment with chemotherapy and novel androgen receptor agents is approved for high volume/risks metastatic prostate cancer.[4-6] However, upfront treatment is not reimbursable in some countries and monotherapy with ADT is the mainstay treatment for those patients. There are several risk factors for the progression to CRPC that have been identified including: serum hemoglobin (Hb) levels, serum alkaline phosphatase (ALP), Gleason grade group, the prostate-specific antigen (PSA) nadir level, the time to PSA nadir (TTN), the neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) ≥150.[7-12]

Therefore, the primary goal of this study is to explore the time duration of disease progression into CRPC, in de novo metastatic prostate cancer patients, post ADT treatment. A secondary aim of this study is to identify risk factors affecting such progression.

Materials and Methods

Study population

This is a retrospective observational study. The patients who were diagnosed with de novo metastatic prostate cancer in our center from January 2008 to December 2019, who received ADT, were retrieved from computer-based medical records. Patient baseline characteristics included: age, body mass index (BMI), and Eastern Cooperative Oncology Group (ECOG) score, mode of ADT, serum PSA level, time to PSA nadir, location and number of bone metastases, pathological report and Gleason (GS) grade group, serum hemoglobin, serum ALP, serum albumin, neutrophil count, lymphocyte count, and platelet count. High-volume disease was defined as the presence of visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis in accordance with CHAARTED Trials.[4]

The exclusion criteria were: patients who underwent local controlling treatment, both radical prostatectomy and radiation therapy or had previous treatment with the chemotherapeutic agents Enzalutamide, and Abiraterone. In addition, patients with no observational investigation evidence including bone scan and/or computed tomography (CT) scan and/or magnetic resonance imaging (MRI) abdomen and pelvis and/or chest radiographic results were excluded. The patients who received chemo-hormonal therapy, ADT plus docetaxel, were also excluded from the study.

Time to CRPC was defined as the time until documented clinical progression or serologic progression with a testosterone level of less than 50 ng/dl.[6] The time to clinical progression was defined as the time lapse until progression to bone metastases and progression according to RECIST, version 1.0.[12] Serologic progression was defined as an increase in the PSA level of more than 50% above the nadir, reached after the initiation of ADT, with two consecutive increases at least 2 weeks apart. The date of a first recorded increase of more than 50% above the nadir was deemed the date of progression. If the nadir level was less than 2 ng/ml, then a minimum increase of more than 2 ng/ml was required.[6]

The institution ethics committee approved the observation protocol and the collection of clinical data for research purposes (Project Number REC.63-193-10-1).

Statistical analyses

Continuous variables are reported as mean±SD or Median (IQR). Discrete variables are presented as number (percentage). The primary endpoint was the time to CRPC of de novo metastatic prostate cancer patients and the secondary endpoint was the risk factors affecting the progression.

CRPC timing was analyzed using the Kaplan-Meier curve and a comparison between the two groups by log-rank test. Finding of risk factors was examined using the Cox proportional hazards model.

Cox proportional hazards regression was used to estimate hazard ratios (HRs) with a 95% confidence interval (CI). Variables associated with $p < 0.2$ in univariate analysis were selected for multivariate analysis. $P < 0.05$ were considered statistically significant. Analyses were performed using the R program version 3.6.1.

Results

Demographic data

Patient characteristics are shown in Table 1, with a total of 125 cases of de novo metastatic prostate cancer patients who received monotherapy treatment with ADT being included in the analysis. The mean age was 69.7 years. Twenty-five patients (20%) were classified as having low volume metastasis while 100 patients (80%) had high volume metastasis. PSA levels in the high and low volume metastasis groups were 500 ng/ml and 215.1 ng/ml respectively. In low volume metastasis patients, 7 (28%) had a GS grade group 1-2, and 18 (72%) a GS grade group 3-5. In the high volume metastasis patients, there were 19 patients (19%) and 81 patients (81%) in GS grade groups 1-2 and 3-5 respectively. Eighty-one patients (64.8%) received a Gonadotrophin-releasing hormone (GnRH) agonist while 42 patients (33.6%) underwent bilateral orchiectomy. Six patients (6%) had visceral metastasis. Twenty-three patients received chemo-hormonal therapy.

Outcomes

The factors related to duration to CRPC are shown in Table 2. Patients in the high-volume cohort had time to CRPC of 12 months compared to 23 months in the low volume cohort ($p < 0.001$)

Table 1. Patient characteristics

	Total N = 125	High volume n = 100	Low volume n = 25	P-value
Age at diagnosis years (SD)	69.7±8.9	69.3±9.0	71.5±8.3	0.255
Body weight (kg) (IQR)	61 (52.0,67.0)	61 (50.0,67.0)	60 (55.0,67.0)	0.491
Height (cm) (SD)	163.7±6.8	163.6±6.9	164±6.6	0.820
BMI (kg/m^2) (IQR)	22.5±3.7	22.3±3.9	22.9±3.0	0.510
ECOG n (%)				0.209
0	83 (66.4)	63 (63.0)	20 (80.0)	
1	32 (25.6)	29 (29.0)	3 (12.0)	
2	10 (8.0)	8 (8.0)	2 (8.0)	
Initial PSA (ng/ml) (IQR)	500 (208.5, 625.0)	500 (304.6, 737.4)	215.1 (78.8, 377.1)	< 0.001
GS grade group n (%)				0.474
1-2	8 (6.4)	19 (19.0)	7 (28.0)	
3-5	18 (14.4)	81 (81.0)	18 (72.0)	
Mode of ADT n (%)				
GnRH agonist	81 (64.8)	63 (63.0)	18 (72.0)	0.543
GnRH antagonist	2 (1.6)	2 (2.0)	0 (0)	1.000
Orchiectomy	42 (33.6)	35 (35.0)	7 (28.0)	0.652
Visceral metastasis n (%)				0.727
Lungs	5 (4.0)	5 (5.0)	0	
Liver	1 (0.8)	1 (1.0)	0	

SD = standard deviation, BMI = body mass index, IQR = interquartile range, ECOG = Eastern Cooperative Oncology Group performance status, GS = Gleason scores, ADT = androgen deprivation therapy, GnRH = Gonadotrophin-releasing hormone

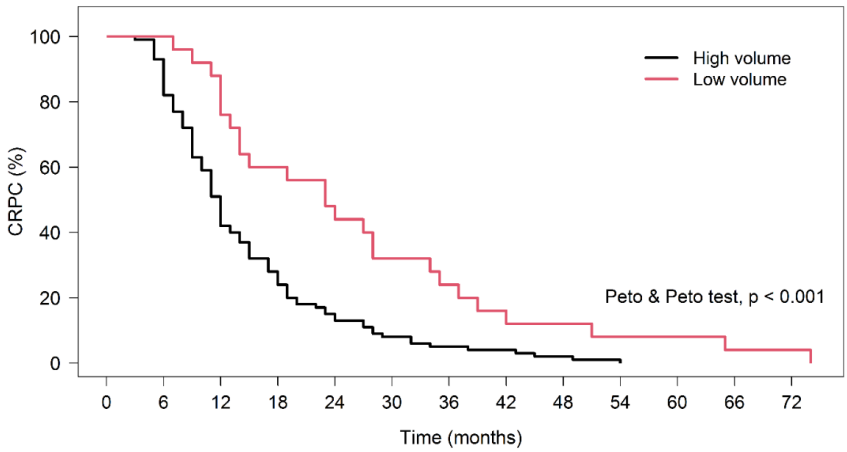

Figure 1. Kaplan-Meier curve of castration-resistant prostate cancer by disease burden

Table 2. Time to CRPC (months) in de novo metastatic prostate cancer patients

Factors	n	Time to CRPC Median (IQR)	P-value
Disease burden			< 0.001
High volume	100	12 (8.0,18.)	
Low volume	25	23 (13.0,35.0)	
GS grade group			0.026
1-2	26	17 (11.2,28.0)	
3-5	99	12 (8.0,19.0)	
Time to PSA nadir			< 0.001
< 6 months	69	7 (6.0,9.0)	
≥ 6 months	86	17 (12.0,27.0)	
Serum Hb			0.549
≥ 12 g/dl	71	12 (8.5,21.5)	
> 12 g/dl	54	12.5 (9.0,21.5)	
PSA nadir level			0.024
< 0.2 ng/ml	8	19.5 (14.2,39.8)	
≥ 0.2 ng/ml	117	12 (9.2,20.0)	
Serum Alb			0.174
≥ 4 g/dl	40	12 (7.0,20.8)	
> 4 g/dl	30	15 (10.2,31.0)	
Serum ALP			0.002
< 350 U/L	45	15 (11.0,32.0)	
≥ 350 U/L	18	8.5 (6.2,12.8)	
NLR			0.584
< 3	68	12 (8.8,22.2)	
≥ 3	57	12 (9.0,19.0)	
PLR			0.885
< 150	56	12 (9.0,19.2)	
≥ 150	69	12 (9.0,23.0)	

GS = Gleason score, PSA = prostate-specific antigen, Hb = hemoglobin, Alb = albumin, ALP = alkaline phosphatase

(Figure 1). The duration in which PSA declined to nadir level was 7 months in the high-volume metastasis group in comparison to 11 months in the low volume metastasis group (p-value =0.011) (Figure 2). Patients with a low GS grade group score (1-2), low serum ALP (< 350 U/L), and/or lower PSA nadir level (< 0.2 ng/ml) had longer time to CRPC. The factors that did not affect the progression of the disease were serum albumin, NLR, and PLR. Time to PSA nadir and time to CRPC in the chemohormanal group were 7 months and 12 months respectively (Figure 5).

The univariate analysis indicated that factors affecting the progression to CRPC were TTN < 6 months (HR 0.15(95% CI 0.09, 0.23), p < 0.001), PSA nadir level ≥ 0.2 ng/ml (HR 2.14 (95% CI 1.02, 4.48), p = 0.025), serum albumin (Alb) level > 4 g/dl (HR 0.74 (95% CI 0.46, 1.2), p = 0.219), and ALP level ≥ 350 U/L (HR 2.83 (95% CI 1.56, 5.1), p = 0.001).

In multivariate analysis, patients with time to PSA nadir < 6 months, high-grade group score (3-4), PSA nadir < 0.2 ng/ml, and high serum ALP ≥ 350 U/L were the independent factors associated with short time progression into CRPC status (Table 3).

When considering factors affecting the progression to CRPC, it was found that the patients with high volume metastatic disease with TTN < 6 months had the shortest time duration with regard to the development of CRPC. This was followed by the patients in the high volume metastatic disease group, with time to PSA nadir level ≥ 6 months and low volume metastatic disease with TTN ≥ 6 months, as shown in Figure 3.

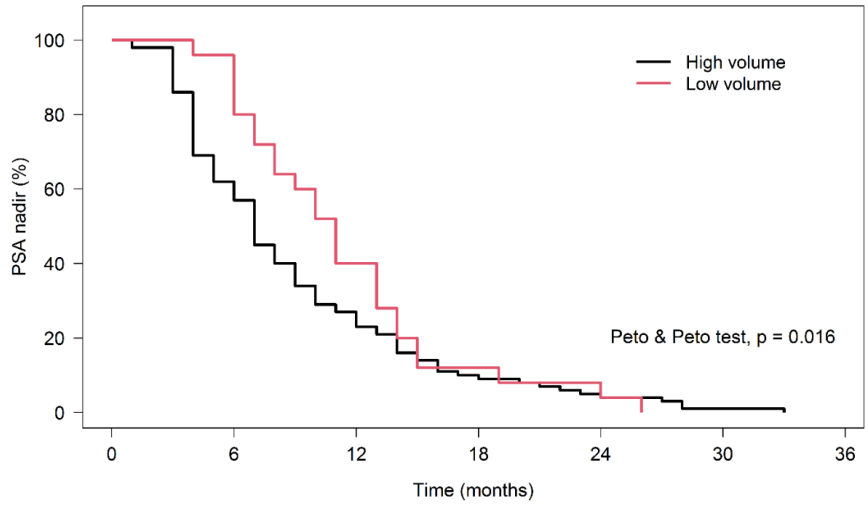

Figure 2. Kaplan-Meier curve of time to Prostatic specific antigen nadir level by disease burden

Table 3. Univariate and multivariate analysis of risk factors affecting the progression to CRPC

	Univariate analysis		Multivariate analysis	
	HR (95% Cl)	P-value	HR (95%Cl)	P-value
GS grade group	1	0.075	1	0.038
1-2	1.47		2.013	
3-5	0.95-2.27		1.04-3.90	
Time to PSA nadir	1	< 0.001	1	< 0.001
< 6 months	0.15		0.053	
≥ 6 months	0.09-0.23		0.02-0.13	
PSA nadir level	1	0.025	1	0.02
< 0.2 ng/ml	2.14		4.487	
≥ 0.2 ng/ml	1.02-4.48		1.27-15.85	
Serum Alb	1	0.219	-	-
≥ 4 g/dl	0.74			
> 4 g/dl	0.46-1.20			
Serum ALP	1	0.001	1	0.002
< 350 U/L	2.83		2.646	
≥ 350 U/L	1.56-5.10		1.42-4.93	

GS = Gleason score, PSA = prostate-specific antigen, Hb = hemoglobin, Alb = albumin, ALP = alkaline phosphatase

However, due to the demographic data of the low volume metastasis disease with TTN < 6 months group, there is only 1 person, therefore it is not possible to find a relationship in the graph. Furthermore, when considering the factors of the GS grade group together with disease burden (Figure 4), it was found that high volume metastatic disease with GS grade group 3-5 resulted in the shortest time to development of CRPC, followed by the high-volume metastatic group with GS grade group 1-2, low volume metastatic disease with Gleason grade group 3-5, and low volume metastatic disease with Gleason grade group 1-2.

Time to CRPC in the low volume, high volume, and high-volume metastasis groups that received chemohormonal therapy was 25, 12, and 12 months respectively (Figure 5). The median time from ADT to chemotherapy was 2.78 weeks.

Discussion

Prostate cancer is one of the most common malignancies in males. Treatment in metastatic prostate cancer aims to prolong overall survival whilst preserving quality of life. For decades, the standard of care (SOC) for metastatic hormone-sensitive prostate cancer (mHSPC) was ADT.[7]

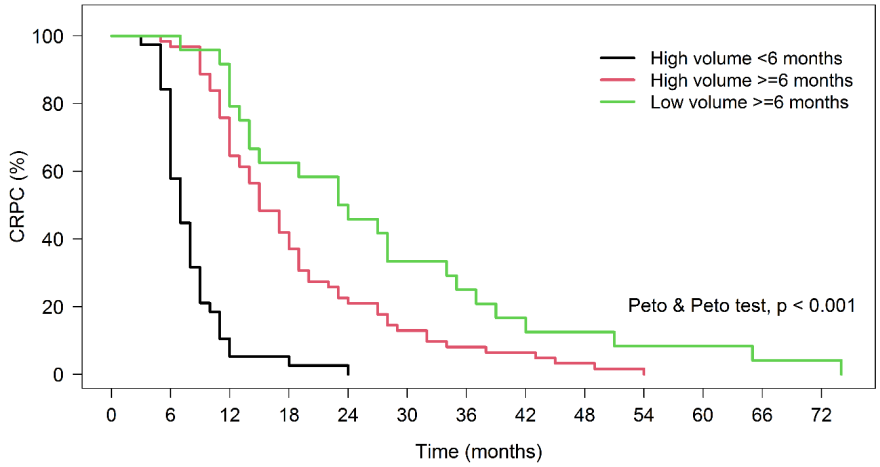

Figure 3. Kaplan-Meier curve of castration-resistant prostate cancer by disease burden and time to prostatic specific antigen nadir level

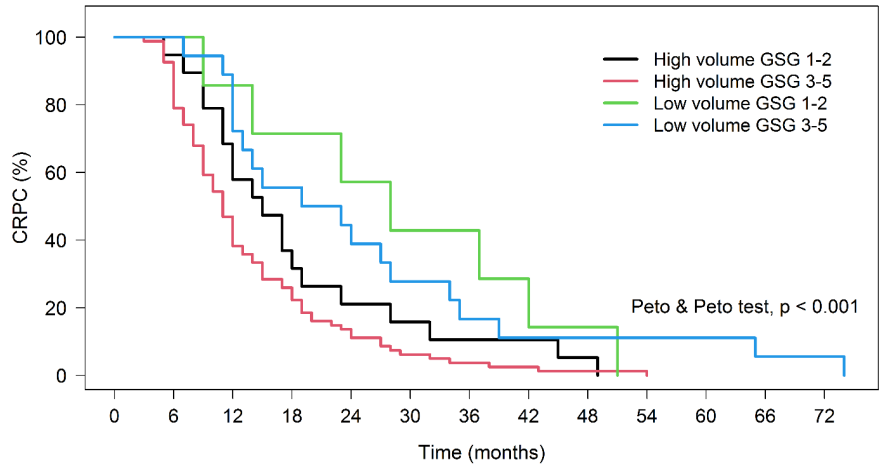

Figure 4. Kaplan-Meier curve of castration-resistant prostate cancer by disease burden and Gleason grade groups

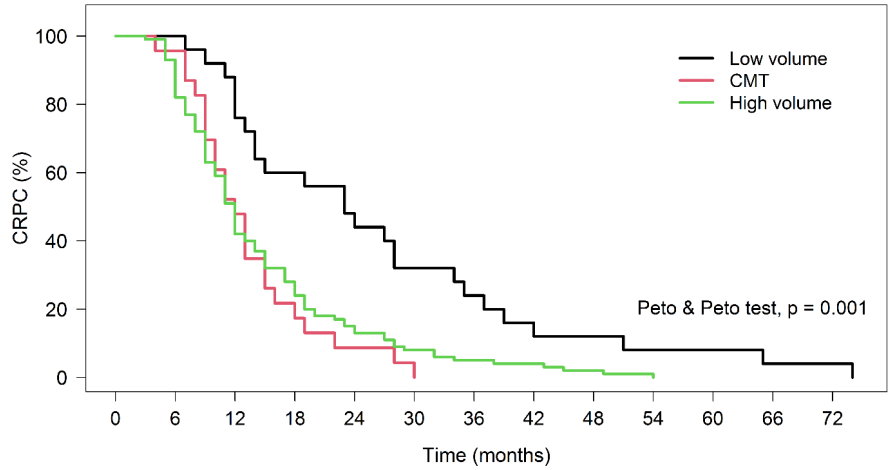

Figure 5. Kaplan-Meier curve of castration-resistant prostate cancer by disease burden and chemohormonal therapy

Over the last 5 years, the treatment landscape has changed dramatically with the addition of systemic agents that have previously been beneficial in the castrate-resistant setting[4]; specifically, docetaxe[8], abiraterone[9], enzalutamide[10,11], and apalutamide.[12] Since that time, many changes have occurred in the treatment of mHSPC. Nevertheless, at some point, all patients will progress to CRPC.

The time duration until CRPC may be a useful tool for the prediction of OS and tumor behavior.[13-18] The main focus of this article is to explore the factors associated with a short duration of disease progression to CRPC.

The time to CRPC, in a study about the combination treatment of Docetaxel plus ADT versus ADT alone in high volume metastatic hormone-sensitive prostate cancer, was reported to be 20.2 months VS 11.7 months,[6] Nevertheless, in Songklanagarind Hospital, the time to CRPC in both groups was 12 months. This is possibly due to the small study population in the combination therapy group (23 patients).

The demographic of high-volume metastatic status in our center looked higher than the previous study, as 80% of patients had high volume metastatic disease.[6,19] Most of the patients developed skeleton-related events or lethal urinary complications during their 1st visit. Forty-two patients (33.6%) received bilateral orchiectomy as their primary ADT. The mode of ADT treatment depended on the patients' health insurance.

PSA is widely used for prostate cancer detection, evaluation of therapeutic outcomes, and predicting prognosis.[20,21] Faster decline in PSA might be associated with cancer related death or transcriptional outcomes from ADT.[22,23] Recent studies demonstrated that a rapid decline in PSA during ADT treatment was a risk factor for the early progression into CRPC.[24,25] Choueiri et al. reported TTN < 6 months and PSA nadir > 0.2 ng/ml had shorter overall survival. Hamano et al. also found that short TTN (< 7 months) and high levels of PSA nadir (> 0.64 ng/ml) were associated with a worse overall survival. Our findings were in agreement with those studies.

Pathology was a strong predictor for OS and time to CRPC. Patients in the higher grade group had a poorer prognosis of progression to CRPC.[26,27] Kongseang et al. revealed that the median time to progression in mHSPC patients treated with ADT, was 37.5, 18.1 and 12.5 months in patients with Gleason scores ≤ 6, 7 and ≥ 8 respectively. In our study, we found a patient with a high GS grade group score (3-5) had a 1.47-fold high risk of progression when compared with a lower GS grade group score (1-2), a finding which was in agreement with a prior study.[10]

ALP is an enzyme primarily found in the liver, bone, intestine, and kidney. It has been associated with bone turnover markers and it has also been used to evaluate the efficacy of treatment in mCRPC.[28] Mikah et al. reported that the dynamic changes in ALP during treatment were associated with better OS in bone metastatic CRPC.[29] Recently, evidence associated with ALP and the prediction of outcomes with regard to mHSPC has been lacking. Our findings suggest that ALP ≥ 350 U/L is associated with poor outcomes.

There was a significantly shorter duration of progression to CRPC after ADT in patients in the high-volume metastasis group. The reason for this may be that the majority of these patients had severe prostate biopsy pathology. The group with a Gleason grade of more than 3, constituted 80% of the patients in this study. Hence, they had a statistically significant shorter duration of PSA reduction to nadir level than the low volume metastasis group. This is thought to be explained by the high expression of androgen receptors in the more severe prostate biopsy pathological group.[14] Nevertheless, the response to ADT treatment was lower.[15]

There are two limitations of this study. The first is due to its 10-year retrospective design, it is dependent on the data collection of several modalities, for example hand-written notes and electronic medical recording (EMR). In addition, there was no standard follow-up or imaging protocol and serum testosterone and blood chemistry were not routinely monitored in our cohort. Furthermore, upfront treatment is not available in Thailand. We believe our data could serve as a guide in making decisions about the proper treatment for patients with metastatic prostate cancer. The second limitation is as all the data is from a single institution the transferability of the findings may be limited. However, the significant nature of the findings warrants a multi-center, larger sample size study in the near future.

Conclusion

Management in metastatic prostate cancer is challenging. Prolonging overall survival and maintaining quality of life are the main clinical aims. Gleason grade group 3-5, time to PSA nadir < 6 months, PSA nadir level ≥ 0.2 ng/ml, and ALP level ≥ 350 U/L were all independent factors found to be associated with poorer outcomes. Thus, close follow-up and upfront treatment is essential in this group of patients.

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