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Clinical and pathological prognostic factors for prostate cancer progression to a castration resistant disease

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ABSTRACT

Prostate Cancers (PC) are one of the few tumors in humans known to be driven by hormones, namely androgens. Androgen Deprivation Therapy (ADT) has long been considered the mainstay management for metastatic PC. Despite initial response to ADT, almost all patient with metastatic prostate cancer will eventually have disease progression marked by a rise in serum PSA level and clinical or radiological evidence of new metastatic lesions, a state termed Castration Resistant Prostate Cancer (CRPC). The aim of the study to study the clinical and pathological factors associated with shorter Progression Free Survival (PFS) in cases maintained on ADT. A retrospective cross-sectional study of 100 patients with metastatic prostate cancer receiving ADT. Patient data were collected at the time of start of ADT and PFS was calculated from the start of ADT until disease progression either biochemical (rising PSA) or clinical/radiological. Studied variables include age, PSA at the start of ADT, time to PSA nadir after start of ADT, Gleason score and metastatic sites. Mean age of the patients was 72.5 ± 10.3 years, mean Gleason score was 7.6 ± 1.2, 80% of patients had PSA > 20, 83% of patients had bone only metastasis and 93% of patients had negative history for use of ADT in the adjuvant setting. The mean progression free survival in the study cohort was 14.5 ± 10.7 months. Pearson correlation test shown that there was a strong negative correlation between Gleason score and PFS (r=-0.62, p<0.001), and time to PSA nadir after start of ADT and PFS (r=-0.3, p=0.003), while there was no correlation between baseline PSA before treatment and progression free survival (p=0.17). The mean PFS shown no significant difference with different age groups (p=0.13), and previous use of ADT (p=0.71), while the mean PFS was significantly higher in patients with only bone secondaries (p=0.002) compared with patients with visceral metastasis. This study demonstrated that higher Gleason grade, longer time to PSA nadir after start of ADT, and, visceral metastasis is associated with shorter time of progression to CRPC. Age, baseline PSA level before start of ADT, and, previous use of ADT in the adjuvant setting does not seem to influence the risk of the progression to CRPC.

Keywords: Castration Resistant PC (CRPC), Androgen Deprivation Therapy (ADT), Progression Free Survival (PFS)

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INTRODUCTION

According to 2017 statistics, 161,360 men in the US are diagnosed with PC and 26,730 men have died from the disease. PC accounts for 19% of non-skin cancers in men and responsible for 8% of male cancer deaths [1]. In Iraq, PC constitute 7.5% of cancers in adults, and, ranks as the fifth most common cancer in males after lung, urinary bladder, leukemia, and colorectal cancer [2].

A recent study on 582 patients with PC from Lebanon, Iraq and Syria have shown that 77.4% presented with organ-confined disease, while, 22.6% presented with stage 4 disease at diagnosis [3]. Androgens are the main drivers for the growth of prostate cancers by binding to and activating the androgen receptor [4]. Hence, Androgen Deprivation Therapy (ADT) h as b een the first-line t herapy f or p atients w ith m etastatic P C [5]. A lso, ADT is an important adjuvant therapy before and/or after surgery or radiotherapy for patients with localized PC who are at intermediate or high risk for recurrence [6]. Since ADT only suppresses the growth of PC cells, it is not curative when used alone, and most patients will eventually progress and become resistant to castration, a state termed, Castration Resistant PC (CRPC) [7]. In a study of many cases with metastatic PC followed for a mean of 3.8 years, 52% had evidence of post-castration progression of disease (17% elevating PSA, 28% presence of ≥ 2 new bone secondaries, 55% met both criteria) [8]. Recurrent Castration-Resistant PC (CRPC) may occur due to aberrant reactivation of the Androgen Receptor (AR). In addition, other mechanisms involving signaling molecules, such as transcription factors, oncogenes, and tumor suppressor genes, may also contribute to PC initiation and progression to incurable disease [9]. Given the poor prognosis of cases with metastatic PC when they enter into the state of castration-resistant disease, identifying clinical predictors of progression to CRPC may help in identifying subsets of patients who may need additional treatments along with androgen deprivation therapy.

The study was designed to examine risk factors associated with shorter progression-free survival in cases with metastatic PC receiving ADT.

METHODS

A retrospective study of 100 cases with metastatic PC on androgen deprivation therapy (LHRH analogue or bilateral orchiectomy).

All enrolled patients have pathologically confirmed PC with radiological evidence of bony and/or visceral metastasis, and taking ADT regularly and under supervision.

Patient's data at the start of ADT includes Age, PSA level at diagnosis, Gleason score, Site(s) of metastasis, previous use of ADT in the adjuvant setting, and, time to PSA nadir.

Patient followed until disease progression which is defined as 3 consecutive rises in PSA 1 week apart, resulting in 50% increases over the nadir, with PSA >2 ng/ml, or radiological progression with castrate serum testosterone level (<50 ng/dl or 1.7 nmol/l), based on the 2017 European Association of Urology guidelines [10].

Statistical analysis was performed using SPSS version 23. Descriptive statistics presented as tables of frequency. Continuous variables were mean ± SD and categorical variables as numbers and percentages. Analytic statistics as ANOVA and student T test were used. Correlation test used to find correlation between two continuous variables. P-value ≤0.05 was considered to be statistically significant.

RESULTS

A total of 100 cases with metastatic PC were enrolled in this work. (Table 1) shows the baseline characteristics at the start of ADT.

Tab. 1. Baseline Characteristics of Patients at the start of ADT (Total no. 100)

Characteristic		% from total
Age (Mean = 72.5 ± 10.3) (Range: (48 - 98) years)	< 60 years	11
	(60 – 69) years	69
	≥ 70 years	20
PSA (ng/ml)	< 10	11
	≥ 10 – 20	9
	> 20	80
Gleason Score (Sum) (Mean = 7.6 ± 1.2)	5	7
	6	9
	7	28
	8	24
	9	29
	10	3
Site of metastasis	Bone only	83
	Bone & Visceral	17
Previous use of ADT (Adjuvant)	Yes	7
	No	93

(Table 2) shows the time to PSA nadir after starting ADT. The mean ± SD time to PSA nadir after the start of ADT was 2.3± 2.1 months. PSA nadir was defined in this study as a PSA value < 0.2 ng/ml similar to a previously published study [11]. (Table 3) shows the Progression Free Survival (PFS) in the study cohort. (Table 4) shows the difference in mean PFS according to age, site of metastasis, and previous use of ADT. The mean PFS showed no significant difference with different age groups (p-value 0.13), and previous use of ADT (p value 0.71), while the mean PFS was significantly higher in cases with only bone metastasis (p-value 0.002)

Tab. 2. Time to PSA nadir after ADT

Time (months)	% from total
≤ 2 months	73
(3 – 6) months	22
> 6 months	5

Tab. 3. Progression Free Survival (Mean = 14.5 ± 10.7 months)

Time (months)	% from total
12 months	52
> (12 – 24) months	22
> 24 months	26

Tab. 4. Mean PFS according to age, site of metastasis and previous use of ADT

Variables		Mean (SD) PFS	P value
Age	<60 years	20.6 ± 13.7	0.13*
	(60-79) years	13.7 ± 9.9	
	≥80 years	14 ± 10.9	
Site of metastasis	Bone only	16 ± 10.5	0.002**
	Bone and Visceral	7.4 ± 8.2	
Previous use of ADT in the adjuvant setting	Positive	16 ± 9.2	0.71**
	Negative	14.4 ± 10.8	

In (table 5), Pearson correlation test shown that there was a strong negative correlation between Gleason score and PFS (r =-0.62, p<0.001) (Figure 1), and time to PSA nadir after start of ADT and PFS (r=-0.3, p=0.003) (Figure 2), while there was no correlation between baseline PSA before treatment and progression free survival (p=0.17).

Tab. 5. Correlation between PFS, Gleason score, TTPSAN and Baseline PSA

Variables	Progression Free Survival (PFS)	
	Pearson correlation	P value
Gleason score	-0.62	<0.001
Time to PSA nadir after start of ADT (TTPSAN)	-0.3	0.003
PSA before the start of ADT	0.3	0.17

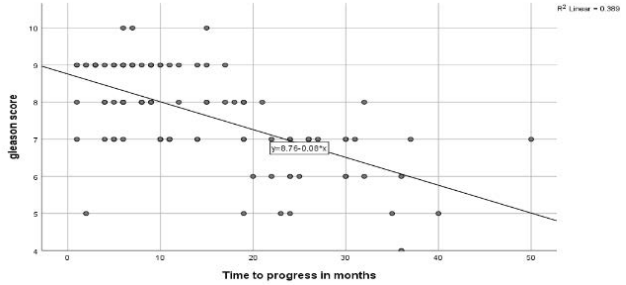

Fig. 1. Pearson Correlation test between PFS and GS

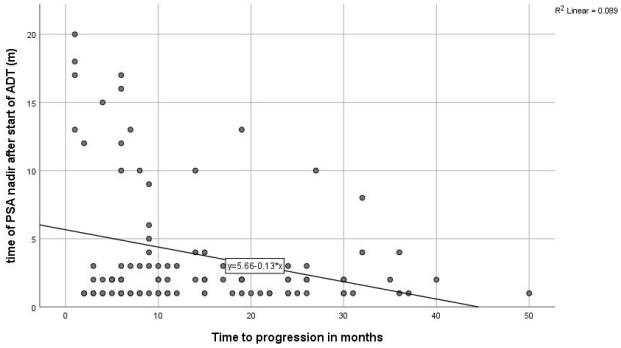

Fig. 2. Pearson Correlation test between PFS and time to PSA nadir after start of ADT

DISCUSSION

The mean age of patients was 72.5 ± 10.3 years, and no significant association was found between age and the PFS (P value 0.13). About 80% of patients have baseline PSA more than 20 ng/ml, and, there was no association between baseline PSA and PFS (P= 0.17).

Yigitbasi et al. studied the prognostic value of age, serum alkaline phosphatase, pretreatment PSA level, GS, and number of bone metastasis foci on the risk of progression to CRPC, and concluded that age and baseline PSA level have no effect on the risk [12]. However, in the study by Nayyar et al., higher PSA level at baseline was associated with poor response to ADT and shorter time to progression to CRCP [13].

In this study, only 7 patients out of 100 patients received ADT as neoadjuvant or adjuvant therapy before the development of metastatic disease, and, although we did not found an association between this variable and the progression free survival (P value 0.71), the small number of patients makes it difficult to draw definite conclusions.

On the other hand, 83% of patient have only bone metastasis while the other 17% have bone and visceral metastasis and there is a significant association between multiple sites of metastasis and progression free survival (P=0.002). These findings correspond

with many previous studies. Gandaglia et al. studied 3857 patients with metastatic PC and investigated the role of metastatic phenotype on cancer specific and overall and concluded that visceral involvement represents a negative prognostic factor and had a significant association with overall and cancer specific mortality (P value<0.001) with respective median overall survival and cancer specific survival of 24 months and 32 months for bone metastasis only and 14 months and 19 months for visceral metastasis [14].

In another study on 440 Korean patients, Kyo et al. found bone metastasis with pain and both bone and visceral metastases showed the worst median progression to CRPC-free and cancer-specific survivals, but this followed by those with bone metastasis without pain. The authors concluded that secondaries spreading and pain patterns confer different prognosis in cases with metastatic PC [15].

Here, the mean Gleason score of the enrolled cases was 7.6 ± 1.2, and, we found a strong association between the GS and progression-free survival (P value <0.001).

These results are in line with many previous studies. In a study from China, Lin et al. analyzed data from 216 cases with metastatic PC who underwent ADT. A total of 121 cases showed progression to CRPC. Multivariate analysis revealed that Gleason grade group, prostate-specific antigen nadir (nPSA), and time to PSA nadir (TTN) were risk factors for progression to CRPC [16].

In another study, Tamada et al. found that a PSA level ≥20 ng/mL, a Gleason score ≥8, and the presence of metastasis at diagnosis were independent predictors of a shorter time to CRPC development [17]. In another study that enrolled 246 patients with PC who received primary ADT, higher tumor grade was found to be an independent factor associated with a shorter time to tumor progression [18].

Although baseline PSA level may have prognostic significance, several recent studies found that rapid response to ADT which can be estimated by nadir PSA (nPSA) and time to PSA nadir (TTN) seem to have better efficacy for prediction of prognosis than baseline PSA [16].

In a study of 650 individuals with advanced (metastatic) PC managed with ADT, Huang et al. reported that both PSA nadir and time to PSA nadir were independent and significant predictors of disease progression. Men with higher PSA nadir (≥0.2 ng/ml) and shorter time to PSA nadir (<10 months) had significant shorter time to disease progression (HR = 3.11, P < 0.001) [19].

In another study of 286 patients treated with primary ADT, Tomioka et al. showed that GS, nadir PSA and time from PADT to nadir were independent prognostic factors for this incidence and lower nadir PSA level and longer time from primary ADT to nadir were good for survival and progression [20]. In our study, we did not find a significant correlation between baseline PSA before ADT and progression-free survival (P value 0.17). However, there was a significant correlation between time to PSA nadir (TTN) after the start of ADT and the PFS (P value 0.003), with prolonged PFS in patients with shorter time to PSA nadir (TTN).

CONCLUSION

In cases with metastatic PC commencing treatment with primary ADT, site of metastasis, Gleason score, and time to PSA nadir (TTN) can be used to predict the risk of progression to CRPC.

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DISCLOSURE

None.

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