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Risk Factors for Prostate Cancer Resistance to First-Line Androgen Deprivation Therapy (ADT)

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Abstract **Original Research Article**

Introduction: Androgen deprivation therapy is the mainstay of systemic treatment for metastatic prostate. However, the majority of patients progress to CRPC. The aim of this study is to identify factors that predict castration resistance in men with locally advanced or metastatic prostate cancer treated with first line ADT. ***Methods:*** This is a retrospective and analytical study including 46 patients treated for advanced or metastatic prostate cancer with first-line ADT at the Military Hospital Mohammed 5 of Rabat (HMMV) between November 2013 and July 2018 (a period of 5 years). The elements analyzed were sociodemographic, clinical, patient history, biological and radiological data. ***Results:*** Predictive factors for castration resistance in our sample are: 1) A high-risk stage according to the LATITUDE criteria. 2) High initial PSA. 3) PSA nadir (PSAn) > 1.17 ng/ml. 4) Elevated PAL at diagnosis > 129 IU/L. 5) Short time to reach PSAn ≤ 9 months. ***Conclusion:*** The risk factors predictive of early resistance to first-line hormonal therapy in patients with metastatic prostate cancer in our series were similar to those described in the literature. We advocate early treatment with hormonal chemotherapy in any patient with metastatic prostate cancer who has any of the elements identified in our study.

Keywords: Castration resistant prostate cancer, risk factors, androgen deprivation therapy, Morocco.

INTRODUCTION

Prostate cancer is an important disease worldwide. It is the most frequently diagnosed malignant tumor in men and the 5th leading cause of death worldwide [1].

In France, 50,000 new cases were diagnosed in 2015 and more than 70,000 in subsequent years [2, 3]. In the United States, new cases of prostate cancer were estimated at 174,650 cases in 2019 [4]. Nationally, prostate cancer was responsible for 3990 new cancer cases in 2018 [5].

These values are constantly increasing, thanks to the aging of the population, with an average age of diagnosis of around 70 years [6], and to early detection through the extension of the systematic measurement of prostate specific antigen (PSA) and the use of prostate biopsies systematized by transrectal ultrasound [7].

In 1941 [8], the American-Canadian physicist Charles Huggins discovered androgen-dependent prostate cancer (CaP). This earned him the Nobel Prize [9, 10]. He considered on the one hand that prostate cancer is influenced by androgen activity and that the metastatic form of this cancer is inhibited by androgen blockade. On the other hand, prostate cancer itself is activated by androgen injections [9].

These deductions revolutionized the world of medicine, proving for the first time that a cancer could be controlled by hormone therapy. Indeed, the homonosensitivity of this tumor allowed scientists to develop a chemical hormone therapy of 1st generation, in particular agonists or antagonists of GnRH (Gonadotropin Releasing Hormone or gonadotropin) whose biological action consists in mimicking that of the physiological neurohormone and in stimulating the synthesis of the gonadotopins [9]: 3 follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the adenohypophysis. These two hormones act on the gonads by activating androgen receptors and lead to the

synthesis of testosterone and its active form dihydrotestosterone (DHT). After some time, the pituitary gland becomes indifferent to GnRH analogues and stops secreting LH. As a result, the production of testosterone by the testicles decreases to zero, this is the stage of chemical castration. This decrease in testosterone levels slows down the growth of prostate cancer cells [11].

Hormone therapy is therefore considered the cornerstone of treatment for metastatic prostate cancer, with its indications expanding to include some cases of localized prostate cancer [12].

Although most patients with metastatic prostate cancer initially respond to hormonal treatment, unfortunately the natural evolution of the disease is towards progression in the vast majority of patients [9, 13]; this is the "hormone-refractory" or "castration-resistant" stage. The latter term is more precise because this cancer remains hormone-dependent despite hormone deprivation.

The aim of our study is to investigate the predictive factors for the development of this resistance to first-line hormonal therapy in 46 patients from the urology department of the Mohammed 5 Military Training Hospital (HMIMV - Rabat).

For this, the following factors were researched and analyzed:

- ✓ age
- ✓ metabolic syndrome (diabetes, high blood pressure, high cholesterol)
- ✓ Toxic history (tobacco, alcohol)
- ✓ Initial PSA, nadir PSA
- ✓ biological factors (CRP, lactate dehydrogenase (LDH), alkaline phosphatase (ALP))
- ✓ the presence of metastases de novo or after radiological or biological progression
- ✓ Time to reach nadir PSA
- ✓ LATITUDE criteria for high-risk metastatic prostate cancer and we compared them to the results in the literature.

MATERIEL AND METHODS

A. Study type

This is a retrospective study including 46 patients collected in the Urology Department of the Mohammed 5 Military Hospital in Rabat (HMMV) over a 5-year period from November 2013 to July 2018. All patients had metastatic prostate cancer undergoing 1st line hormone therapy.

Data collection was ensured by an exhaustive search of the medical records, radiological and anatomopathological reports available in the archives of the Urology and Oncology departments of the HMMV.

Collected were:

- ✓ age
- ✓ Background:
  - Medical: diabetes; hypertension; hypercholesterolemia; cardiovascular
  - Surgical
  - Toxic substances (smoking and alcohol)
- ✓ Paraclinical data : PAL, LDH, CRP, initial PSA.
- ✓ Classifications and scores : Gleason score of the prostate biopsy, DAMICO stage, TNM classification.
- ✓ The type of treatment received.
- ✓ PSA nadir, Testosteronemia
- ✓ The time to reach PSA nadir

The aim of the study is to identify risk factors predisposing to early resistance to castration. Based on the average time of two years, reported in the literature by different studies (Axel S Merseburger *et al*., [15], T Karantanos [16], Silvana Giacintia [17]) to progress to CPRC. A resistance time of 2 years was considered as a reference to analyze the incrimination of risk factors in the predisposition to CRPC. Furthermore, any resistance before 2 years was defined as early resistance and after 2 years as late resistance.

To analyze the two biological parameters (initial PSA and nadir PSA) and the time to reach nadir PSA, the median value of each of these factors was used. Thus, the median value of:

- ✓ Initial PSA : 150 ng/ml
- ✓ PSA nadir : 1.17 ng/ml
- ✓ Time to reach nadir PSA : 9 months

In order to analyze the role of advanced age in early resistance to castration, a value of 75 years was set, corresponding to the recent definition [18] of the elderly subject.

The impact of metastasis was analyzed using the LATITUDE criteria to stratify patients into low and high risk.

B. Inclusion and exclusion criteria

1. Inclusion criteria:

We included any patient with metastatic prostate cancer who had received 1st line hormone therapy for which he or she had biological or radiological castration resistance.

2. Exclusion Criteria:

CRPC treated with 2nd line hormonal therapy or chemotherapy.

3. Study population:

Of the 54 files that were studied, 46 were selected according to the above-mentioned criteria.

C. Method of data collection:

1. The operating sheet:

The data collection was carried out on a pre-established questionnaire

2. Research Method :

The search was performed using the search base present on the library of :

- Medline
- Pub Med
- Hinari
- Direct science and
- Clinical Key
- African Index Medicus

Using the following keywords :

- Prostate cancer
- Prostate Cancer Screening
- Diagnosis of prostate cancer
- Metastatic prostate cancer
- Androgen receptor and prostate cancer
- Castration-resistant prostate cancer (CRPC)
- Management of metastatic prostate cancer
- First-line hormone therapy and metastatic prostate cancer
- New therapies for metastatic prostate cancer

3. Statistical analysis:

Data entry and analysis were performed using SPSS 23 for IOS (IBM corporation, ARMONK, NEW YORK, U.S).

Regarding the data analysis, two typologies of analysis were chosen:

- Univariate analysis: which only serves to describe the different variables involved in the study.
- Bivariate analysis: the study of the relationship between two variables deemed useful to support the results of our study.

Categorical variables were described in numbers and percentages, and the comparative study was performed by Pearson's Chi-Square percentage comparison method or by the Fisher Exact method (in case the expected number of people was less than 5 in the Chi-Square method). A $P < 0.05$ was considered statistically significant.

RESULTS

A. Descriptions:

1. Total number of patients:

- For our study we collected 46 patients with metastatic castration-resistant prostate cancer;
- Age distribution : The average age of our patients at diagnosis was 74 ± 9.2 years (57-92 years).
- The analysis of the distribution of patients was divided into two categories (Figure 1). Our sample consisted of two analytically similar categories. Thus, twenty-three patients (or 50%) were in the age range below 75 years and twenty-three patients were 75 years or older.

2. Distribution by terrain:

a) Personal History:

- 41.3% of our patients (n=19) had associated chronic diseases. The most frequent medical history reported was hypertension and diabetes with 34.8% (n=16) and 21.7% (n=10) respectively. A total of 21 patients had a metabolic syndrome characterized by a cluster of disorders including hypertension, insulin resistance, overweight with central obesity, and dyslipidemia.
- Regarding toxic history, 23.9% (n=11) were smokers and 8.7% (n=4) were enolics. Ten patients (21.7%) were operated for trans-urethral resection of the prostate, two patients for cataract (4.34%), two patients for valvulopathy (4.34%), one patient for herniated disc and one patient for inguinal hernia.

b) Family history:

In our series, 3 cases had a history of prostate cancer or breast cancer (6.5%).

3. Diagnostic Timeframe:

The mean time from onset of symptoms to clinical diagnosis was 47.6 ± 46.93 days (7-240 days).

4. Clinical examination :

The patients in our study reported different symptoms at the first consultation. These functional signs were subdivided into:

- Dysuria in 34.8% of cases (n=16)
- Pelvic pain with a rate of 8.7% (n=4)
- Hematuria in 4.3% of patients (n=2)
- Asymptomatic in 52.2% of cases (n=24)

5. Paraclinical parameters :

a) Initial PSA :

- The initial PSA was indicated in 38 of 46 cases. The minimum PSA value in our series was 9.96 ng/ml, the maximum was 9650 ng/ml with a mean level of 723.45 ng/ml.
- The results analyzed are divided into 2 groups according to the median PSA value of the sample which is 150 ng/ml :
  - ≤ 150 ng/ml
  - > 150 ng/ml

b) Gleason Group :

For the distribution based on the patients' Gleason group, the results are as follows :

- 2.6% of patients were classified as group 1 (n=1),
- 15.4% (n=6) in group 2,
- 15.4% (n=6) were classified as group 3,

- 38.5% (n=15) were classified as group 4 and
- 28.2% of patients (i.e., n=11) had a group 5.

c) Alkaline phosphatase PAL:

- In our series, alkaline phosphatase was noted in 12 charts (26% of patients). The mean value was PAL = 405.72 IU/L (84-2200 IU/L)
- The results are divided into 2 categories according to the normal value of PAL.
  - ≤ 129 IU/L: 5 patients
  - > 129 IU/L: 7 patients

d) Lactate dehydrogenase LDH:

There were only 2 patients in our study sample who had the LDH value listed on their records. The two values were 119 IU/L and 485 IU/L.

e) Biopsy length of the tumor:

- Biopsy length of the tumor was indicated in 41% of patients (n=19). A mean value of 62% was reported on biopsy reports (10-100%).
- The results are divided into 2 groups according to the median value of the biopsy length of the tumor in our study, which is 50%:
  - ≤ 50%: 8 patients
  - > 50%: 11 patients

f) PSA nadir:

The mean nadir PSA level in our study was 46 ng/ml with a minimum of 0.08 ng/ml and a maximum of 1100.73 ng/ml.

g) Time to reach nadir PSA (PSAn):

The average time to reach the PSA nadir is 10 months +/- 7, with extremes ranging from 2 to 36 months.

h) Resistance-free survival time:

The mean time to castration-free survival was 15.76 months +/- 8.98 (7-58 months).

i) Presence of de novo or post-progression metastases:

63% (n=29) had novo metastatic prostate cancer versus 37% (n=17) who had progressed after local treatment, proven by pelvic MRI / CT scan / bone scan / choline PET scan performed as part of an extension workup.

B. Analytical

1. Age-dependent resistance of prostate cancer to castration:

- In order to analyze the effect of the age factor on the resistance of prostate cancer to first-line hormone therapy, we stratified the sample age into 2 categories : Age less than 75 years and age greater than or equal to 75 years.
- 68.2% of patients under 75 years of age developed castration resistance within 2 years compared to 57.9% of patients over 75 years of age ($p < 0.05$). This difference was not significant, so advanced age is not a risk factor for resistance in our study.

2. Prostate cancer resistance to castration in relation to patient history:

a) Hypertension:

- Of the 16 patients who reported AH, 4 had missing data.
- 50% (n=6) of hypertensive patients resisted castration before 2 years compared with 69% (n=20) in non-hypertensive patients, with no significant difference retained.

b) Diabetes:

- Only 6 diabetic patients had a resistance delay on their records for statistical analysis.
- Resistance to early castration was similar in diabetic and non-diabetic patients (66.7% and 62.9% respectively) with a non-significant difference (p=0.62).

c) Metabolic syndrome (metabolic sd):

- 17 patients had reported the existence of one of the components of the metabolic syndrome characterized by a set of disorders including hypertension, diabetes, overweight with gynoid obesity, and dyslipidemia.
- There was no significant difference in the early resistance to castration in patients with metabolic syndrome compared to those without metabolic syndrome (p=0.53).

d) Cardiovascular history :

- 6.5% (n=3) of patients had a cardiovascular history.
- There was no significant difference between patients with and without a cardiovascular history in early resistance to castration (p=0.7).

e) Smoking:

- In our study, 23.9% (n=11) were smokers but only 9 of them had the notion of the resistance period mentioned on their records.
- Data analysis did not show a statistically significant difference between the two groups (p=0.273).

f) Alcohol:

- 4 of 46 patients with resistance to first-line hormone therapy had enolic habits.
- Statistical analysis showed that 63.2% (n=24) of the patients without a history of alcohol resisted castration early. An almost similar incidence was observed in the group of patients with a history of alcohol with a rate of 66.7% (n=2). The difference was not significant (P=0.7).

3. Prostate cancer resistance to castration based on positive diagnostic data

a) Diagnostic Timeframe:

- To clarify the exact time from the onset of symptoms to confirmation of the diagnosis, the time from the first consultation to obtaining histological evidence was calculated. This time was determined for 29 of 46 patients in our study. A time of 47 days, corresponding to the mean value of our sample, was designated for statistical purposes.
- The Chi-square test was replaced by the Fisher statistical test because it was not applicable. The statistical analysis did not report a significant difference in the incidence of early resistance of prostate cancer to first-line hormone therapy based on a long diagnostic time of more than 47 days or a short one of less than 47 days.

b) Histology data : LATITUDE risk classification :

Table 1: Incidence of risk-based castration resistance according to latitude

LATITUDE	Incidence	The resistance		Fisher exact P < 0,05
		≤ 2 years	> 2 years	
Low risk	20	45 % n=9	55 % n=11	< 0,05
High risk	20	85 % n=17	15 % n=3	
Total	40			

85% (n=9) of patients classified as high-risk developed resistance symptoms within the first two years of treatment with first-line hormone therapy. This compares with only 45% in the low-risk category. Statistically this difference is highly significant (p=0.009).

4. Prostate cancer resistance to castration as a function of initial PSA, nadir PSA, and time to reach nadir PSA:

a) Initial PSA :

Table 2: Incidence of castration resistance according to initial PSA level

Initial PSA in ng/ml	Incidence	The resistance		Khi deux test P < 0,05
		≤ 2 years	> 2 years	
PSA ≤ 150	19	47,4 % n=9	52,6 % n=10	< 0,05
PSA > 150	14	92,9 % n=13	7,1 % n=1	
Total	33			

The vast majority of patients with an initial PSA level above 150ng/dl at diagnosis developed resistance to first-line chemical castration within two years with an incidence of 92.9% (n=13). In the group of patients with a level less than or equal to 150ng/ml an incidence of 47.4% (n=9) was noted and about half of this group showed signs of early resistance. The difference was statically highly significant.

b) PSA nadir:

Of a total of 46 records, 34 contained evidence of the patient's nadir PSA value.

Table 3: Incidence of castration resistance according to nadir PSA level (ng/dl)

PSA in ng/ml	Incidence	The resistance		Fisher exact P < 0,05
		≤ 2 years	> 2 years	
PSA ≤ 1,17	16	43,8 % n=7	56,3 % n=9	< 0,05
PSA > 1,17	18	83,3 % n=15	16,7 % n=3	
Total	34			

The incidence of early resistance to first-line hormone therapy was 83.3% (n=18) in the group of patients with a nadir PSA exceeding 1.17ng/ml versus 43.8% for nadir PSA values less than or equal to 1.17ng/ml. This represents a statically significant difference (p=0.019).

c) Time to reach nadir PSA

The statistical results of this group revealed that 93.8% (i.e. n=15) of the patients who reached nadir PSA in a period of no more than 9 months resisted castration early compared to 40% (n=6) for patients who took more than 9 months to reach nadir PSA. A significant statistical difference was noted (p=0.002).

Table 4: Incidence of castration resistance according to time to reach nadir PSA (months)

Time to reach nadir PSA	Incidence	The resistance		Fisher exact P < 0,05
		≤ 2 years	> 2 years	
≤ 9 mois	16	93,8 % n=15	6,2 % n=1	< 0,05
> 9 mois	15	40 % n=6	60 % n=9	
Total	31			

5. Prostate cancer resistance to first-line hormone therapy as a function of biological factors:

a) Alkaline phosphatase (ALP):

Table 5: Incidence of castration resistance as a function of alkaline phosphatase (ALP) (IU/L)

Alkaline phosphatase (IU/l)	Incidence	The resistance		Fisher exact P < 0,05
		≤ 2 years	> 2 years	
≤ 129	5	40 % n=2	60 % n=3	< 0,05
> 129	7	100 % n=7	0 % n=0	
Total	12			

All patients with PAL levels greater than 129 IU/L at diagnosis resisted castration early with an incidence of 100% (n=7), compared to only 40% of patients with initial PAL levels less than or equal to 129 IU/L. Statistically, this difference is highly significant (p=0.045).

b) Prostate cancer resistance to castration in de novo metastatic patients compared to patients who progressed on local therapy :

63% (n=29) of our patients had de novo metastatic prostate cancer and 37% (i.e. n=17) had radiological progression after local treatment. Only 27 patients with de novo metastatic prostate cancer had the notion of the resistance time on their records. This is also the case for patients with metastatic prostate cancer with radiological progression, only 14 records had the notion of resistance time.

This difference was not statically significant (P=0.173).

Table 6: Incidence of early castration resistance according to different parameters

Variables		Number	Incidence or early resistance	P		
				Khi deux of Pearson	Fisher exact	Sig.
Age		41		0,360		NS
	≤ 75 years		68,2 % (7)			
	> 75 years		57,9 % (11)			
Background	Diabetes	41	66,7 % (4)		0,622	NS
	High blood pressure	41	50 % (6)		0,213	
	Hypercholesterolemia	40	100 % (1)		0,634	
	Cardiovascular	41	68,7 % (2)		0,701	
	Tabacco	41	77,8 % (7)		0,273	
	Alcohol	41	66,7 % (2)		0,701	
	Metabolic syndrom	41	58,8 % (10)		0,530	
Clinic	Time to diagnosis	29			0,07	
Histology	Latitude risk	40				***
Biology	Initial PSA > 150	33				***
	Nadir PSA > 1,17	34				
	Time to reach nadir PSA < 9 mois	31				
	Alkaline phosphatase	12				
Novo or post progression metastases	Novo	27				NS
	Post progression	14			0,173	

NS = Not significant; *** = Highly significant

DISCUSSION

A. Introduction:

- At the time of diagnosis, 77% of prostate cancer cases are localized; 13% have a secondary lymph node location and 6% have distant metastases [19]. The 5-year relative survival rate for localized and regional prostate cancers is 100%, compared to 30.5% for metastatic cases [29].
- There are two forms of metastatic disease:
  - De novo metastatic disease: the patient is metastatic at the time of diagnosis
  - Metastatic disease that has progressed after local treatment.
- First-line hormone therapy is indicated as the initial treatment, however after the initial response, almost all patients will eventually progress biologically or clinically. At this stage, the disease is called castration-resistant prostate cancer (CRPC). The median survival for CRPC is in the range of 15 to 36 months, although exact survival rates vary depending on the amount of metastatic disease.
- CRPC is a chronic disease. Treatment at this stage is aimed at delaying the onset of symptoms, improving survival and quality of life.
- Epidemiologic information on CRPC, however, is scarce. In an English retrospective cohort study in 2012 [52], in a population of 11,600 prostate cancer patients, 3277 (28%) had developed CRPC during the study period, with an incidence rate of 8.3 /person-years. Another French cross-sectional study estimated the prevalence and incidence of mCRPC to be 62 and 21 cases per 100 000 men, respectively, in 2014 [20].

B. Key facts :

- Our study is in line with the literature in terms of sociodemographic, clinical and biological data of patients with CRPC. Our study did not statistically demonstrate that advanced age exposes to early resistance to castration especially since the incidence was found to decrease with advanced age which is supported in many studies.
- In addition, two biological parameters in our patients were statistically significant : the initial PSA and the nadir PSA. This is consistent with the results of the literature.

C. Comparison with the literature:

1. Epidemiology:

Age at diagnosis:

- The mean age of our patients was 74 ± 9.2 years, which is close to the data in the literature, which reports a mean age of 65 years in patients with CRPC. The Sofia España study [21] recorded a mean age identical to our study 74 ± 9.2 years. The study by Ting-Ting Lin *et al*., [22] had noted a mean age of 70 ± 8.15 years.
- Our study did not find a significant association between advanced age and the occurrence of early castration resistance ($p < 0.05$) although a decrease in the incidence of castration resistance with advanced age was noted. This was noted in the study by Kumar Sureka [23] and Smaletz *et al*., [24]. These authors found that advanced age was associated with delayed development of castration resistance. Nevertheless, it is preestablished that advanced age (≥ 75) is associated with poor overall survival.

Diagnostic Timeframe:

- The average time to diagnosis in our study was 47.6 days. This mean time is close to that found in the literature. In the United Kingdom, it was 56 days and in a Canadian study it was 53 days. Our study did not show a significant association between a diagnosis time? 47 days, > 47 days and early resistance to castration ($p = 0.07$) although there is an increasing numerical trend towards early resistance to castration with a short diagnosis time ≤ 47 days.
- In the literature, delay in diagnosis has not been linked to progression of prostate cancer to castration resistance. However, two studies [25, 26] on prostate cancer had reported a positive association between long delay in diagnosis and survival/mortality.
- Delay in diagnosis is important not only for clinical reasons, but more importantly for its psychological implication on patients. The experience of waiting can have other deleterious effects on prostate cancer patients, including anxiety and sexual dysfunction [27].

Background:

- In our series, the most frequent medical comorbidities were arterial hypertension (34.8%) and diabetes (21.7%). Hypercholesterolemia, BMI >25, and cardiovascular history were reported in 2.2%, 15.2%, and 6.5% of cases.
- Chronic smoking was found in 23.9% of our patients (n=11), while 8.7% of patients were enolics.
- Our study found no statistically significant association between the existence of a metabolic syndrome and predisposition to early resistance to medical castration ($p < 0.05$). However, in the retrospective study by J. Flanagan *et al*., [28] the authors showed that the different components of the metabolic syndrome, including BMI > 30, hypertension, low fasting HDL and diabetes, had a statistically significant effect on the time to progression of PSA in the multivariate analysis. In the same sense, a recent American study had noted that metabolic syndrome is a risk factor for early development of CRPC and that statin use is a protective factor against CRPC [29].

- In the study by Daniel E. Spratt [30], the authors demonstrated a decrease in the development of castration-resistant prostate cancer in diabetic patients on metformin compared to diabetic patients on other oral antidiabetic agents (p = 0.01).
- Our sample did not show that exposure to tobacco or alcohol was associated with a higher risk of developing CRPC. However, in the literature, chronic smoking is closely linked to the early development of biological recurrence and CRPC. This is the case in the study by Moreira *et al*., [31], where they found a trend toward increased risk of CRPC in active smokers. Indeed, the risks of developing CRPC in smokers were almost 2.5 times higher than in nonsmokers.

2. Biological tests:

Initial PSA :

- The mean PSA in our series was 723.45 ng/ml, and 42.1% of patients had a PSA level >150ng/ml at diagnosis. These figures were higher than those found in the study by Yamada et al32 where the mean initial PSA level was 334.94 ng/ml/.
- In our study, we statistically proved the existence of an association between an initial PSA >150ng/ml and the occurrence of early castration resistance (p < 0.05). In the same sense Kumar Sureka [33] noticed that a high initial PSA is a predictive factor of castration resistance (p = 0.01). Similar to our study, Yamada *et al*., [32] had noted that a high PSA at diagnosis was significantly related to a poor response to first-line hormone therapy (P<0.037) which leads to progression of metastatic prostate cancer to mCRPC. However, this was not the case in a retrospective analytical study performed in the urology and oncology departments of the Military Hospital of Meknes [14] which did not find a significant relationship between an initial high PSA and a risk factor for early resistance to castration.

Table 7: Comparison between our series and the literature according to the mean initial PSA level

	Our series	**Yamada *et al*., [32]**	**Kumar Sureka [33]**	**Study of the HM of Meknes [14]**
Average initial PSA level (ng/ml)	723,45	334,94	135	213,9
Survival time in castration resistance (months)	15,76	10,3	17,7	16,25
P	< 0,05	< 0,05	< 0,05	NS

Risk stratification by LATITUDE criteria:

- Our study found a highly significant association between patients classified as high risk according to LATITUDE criteria and early progression to castration resistance (p=0.009).
- This was also reported in a Belgian study that noted that a high-risk stage according to the LATITUDE criteria is able to predict early progression to castration-resistant prostate cancer and overall survival [34].

PSA nadir:

- The mean nadir PSA level in our sample was 46.25 ± 187.83 ng/ml. This value is still high compared to the literature. Jiang [38], in his study had noted a mean nPSA of 24.45 ng/ml. Similarly, Lin [36] found a mean nSAP of 3.23 ng/ml and Huang [37] found a nSAP of 0.19 ng/ml.
- Our study found a statistically significant association between PSAn > 1.17 ng/ml and rapid progression to castration resistance (P<0.05). In the same direction, Lin [36] had also shown that PSAn >0.2 ng/ml was associated with poor progression-free survival compared with PSAn > 0.2 ng/ml (P<0.001). Progression-free survival was lower in patients with higher PSAn. Huang [39] similarly had proven that patients with higher PSAn had a significantly higher risk of prostate cancer progression to CRPC compared with those with lower PSAn (P<0.001).
- Jiang *et al*., [38], in his study had shown that patients with higher nSAP were more likely to progress to CRPC (P<0.001). This could be explained by the rapid elimination of hormone-sensitive prostate cancer cells, which induces a favorable environment for cell growth leading to CRPC [35]. In addition, rapid suppression of the androgen receptor may have a negative impact on disease progression, as the androgen receptor may act as a tumor suppressor [39].

PAL:

- In our study, we noted a mean PAL level of 405.72 IU/L. This average level is very high compared to those found in the literature. Lv Wei [40] and Jiang [41], report in their studies a mean PAL level of 96.5 IU/L and 98 IU/L respectively. The statistical analysis divided our patients into two groups (≤ 129 IU/L, >129 IU/L).
- In a Chinese uni-variate and multivariate analysis, Wei [42] had deduced that a high initial LAP value is a prognostic factor for the time to progression to CRPC in medically castrated patients (p < 0.001). Similarly, Jiang [43] and Mori [44] had concluded that a high initial LAP was statistically highly related to the rapid progression to CRPC.
- Our study confirms the finding in the literature. It was found that a LAP > 129 IU/L at diagnosis is associated with early resistance to castration. It has also been shown that in patients with CRPC, high

baseline LAP levels were associated with worse outcomes including progression to general deterioration, skeletal complications and decreased survival. In addition, high LAP levels correlated with extensive metastatic bone disease [44].

LDH:

- The LDH value could not be statistically analyzed in our study due to insufficient data. However, in the literature a high LDH value at diagnosis is strongly related to progression to CRPC.
- This was proven in a multivariate analysis [45] which showed that high LDH expression was a significant predictor of time to onset of castration resistance ($p = 0.02$). Another Japanese multivariate analysis [46] showed that LDH level was a significant predictor of patients whose primary androgen deprivation therapy was judged to be a treatment failure. Therefore, LDH adds additional prognostic value and may be useful in recognizing patients who need aggressive treatment after castration failure.

3. De novo metastases/metastases after progression:

- Our patients were divided into 2 groups (de novo metastases, metastases after progression). No statistically significant relationship was demonstrated in our study between the presence of metastases (de novo or after progression) and rapid progression to CRPC ($p=0.173$).
- Our series agrees with the findings in the literature. Guo-Wen Lin [47] had noted that lymph node involvement and distant metastases were not related to castration-free survival.
- However, Cho [48] had found in his study that the presence of distant lymph node metastases was a significant prognostic factor in reducing the time to progression to CRPC.

4. Time to reach nadir PSA:

- The mean time to reach nSAP in our study was 10.58 ± 7.33 months. This time did not differ significantly from those reported by Ji [49] and Lin [36] with mean times of 9 months and 8.10 months, respectively.
- Within our study, we proceeded to divide the patients into 2 groups according to the time to reach nSAP (≤ 9 months, > 9 months). As a result, there was a statistically significant association between a short time to reach nSAP and the occurrence of early castration resistance ($p < 0.05$).
- Our results were similar to those of Lin [36], Jiang [38], Akbay [50] who also found that a short time to reach nSAP was significantly associated with rapid progression to CRPC ($p < 0.001$). Another Chinese uni-variate and multivariate analysis [51] statistically demonstrated that patients whose PSA decreases rapidly during the initial phase of hormone therapy are more likely to progress to CRPC.
- Nevertheless, two studies [51, 14] found that a longer time to reach nSAP was associated with a higher risk of developing CRPC.

Conclusion and limitations of our study

Metastatic prostate cancer is a complex entity in its various components, starting from the concept of the hormone-dependent development of this tumor, its initial positive response to treatment and its subsequent ability to adapt to an androgen-free environment. Despite the numerous therapeutic arsenals for the management of metastatic prostate cancer, the disease progresses to castration resistance.

The poor prognosis of patients with CRPC justifies new therapeutic strategies that seek to personalize treatment according to each patient's status in order to improve their quality of life and overall survival. A better understanding of the common baseline risk factors among patients with CRPC has become a necessity today. Indeed, it would allow to optimize the treatment in such a way as to adapt to each profile, defect and to avoid the harmful side effects generated by hormone therapy.

According to our study, the predictive factors for castration resistance would be:

- A high risk stage according to LATITUDE criteria
- High initial PSA
- PSA nadir (PSAn) > 1.17 ng/ml
- Elevated PAL at diagnosis > 129 IU/L
- A short time to reach PSAn ≤ 9 months

These factors are essential in the management of each case of CRPC. The treating physician, taking into account these elements, could accelerate management by proposing hormone replacement therapy for each patient with an initial PSA of more than 150 ng/mL and/or a PAL of more than 129 IU/mL and/or a high-risk metastatic CaP. The managing physician (ECP) could also suggest more frequent visits to monitor the nadir PSA over time.

Study Limitations: The statistical analysis of our work had some limitations :

- The sample size
- Lack of data on certain risk factors

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