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Prognostic Value of Progesterone Receptor Status in Metastatic Prostatic Adenocarcinoma

Amal Sayed Ahmed[*!], Magda Elsayed Hassan Allam[2], Wafaa El-Beshbishi[3], Mona Abdel Rahim[4], Mohamed Saad El-Ashry[5]

1. Assistant lecturer, Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Mansoura University, Egypt.* Amal_sayed_ahmed@yahoo.com
2. Professor, Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Mansoura University, Egypt.
3. Professor, Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Mansoura University, Egypt.
4. Professor, Pathology Department, Urology and Nephrology Center, Mansoura University, Egypt.
5. Professor, Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Mansoura University, Egypt.

Email: Amal_sayed_ahmed@yahoo.com

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Abstract: De novo metastatic disease at the time of initial diagnosis is considered as a poor prognostic factor in prostate cancer patients. Progesterone receptor (PR) status and its prognostic value in patients with metastatic prostatic adenocarcinoma is still a matter of controversy. This study aims to define this issue and if it affects patient prognosis. It is a cohort study that was conducted in Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital. It included 50 patients diagnosed with metastatic prostatic adenocarcinoma. Histopathological examination of the biopsies was confirmed and PR status was assessed using immunohistochemistry (IHC) as a primary end point of the study. Clinicopathological, treatment and survival data were collected. PR status and clinicopathological parameters were correlated to the patient's survival. This work revealed PR positivity in nearly half of the cohort study cases (48%). Patients with positive PR had statistically insignificant better OS with restricted mean survival time (RMST) at 24 months of 22.7 vs. 21.7 months (P= 0.2) and PFS with RMST at 24 months of 19.6 vs. 17.3 months (P= 0.16). In conclusion, although it has not been proven to have a statistically significant prognostic value, this study has confirmed PR positivity in some cases that may raise the possibility of a new hormonal pathway that could be targeted in the metastatic prostatic adenocarcinoma.

Keywords: *Metastatic prostatic adenocarcinoma, Progesterone receptors, Immunohistochemistry, Survival.*

Introduction

Prostate cancer (PC) is known as one of the most common cancers in men in the world, and a leading cause of cancer mortality in male patients according to GLOBOCAN 2020 database. It is the second most common cancer in men after lung cancer and the fifth most common cause of cancer-related death among men, with 375,000

deaths (3.8%) in 2020 **(Sung et al. 2021)**. Metastatic PC at diagnosis represents 5% of new cases in some Western countries up to 60% in some areas in East Asia **(Siegel et al. 2018)**.

In Egypt, prostate cancer is the fourth most prevalent cancer among men. In 2022, it is estimated to account for 5181 (7%) of the cancer new cases with 2102 deaths that came in the 11th rank of all cancer deaths (2.2 %) **(WHO 2022)**

Egyptian men with prostate cancer have baseline poor prognostic features such as higher prostate-specific antigen (PSA), PSA density and higher Gleason grade at initial diagnosis. The most of the cases occur at the 7th decade of age **(Elabbady et al. 2014)**.

De novo metastatic disease at the time of initial diagnosis is considered as a poor prognostic factor in prostate cancer patients **(Posdzich et al. 2023)**. It is estimated to have a 5-year survival rate of 30% **(Mattiuzzi and Lippi 2019)**. Androgen deprivation therapy (ADT) represents the basic treatment in metastatic prostate cancer as a main component of various newly approved combination therapies. However, emerging of castration-resistant prostate cancer (CRPC) raises the importance of searching for alternative hormonal therapies that could delay the development of CRPC. Well-established prognostic value for PR status has been declared in breast cancer patients. Based on being hormonal-dependent diseases, we got the idea of the possible application of this concept in prostatic adenocarcinoma. We selected to study de novo metastatic disease because it is identified as a poor prognostic factor trying to suggest a new therapeutic pathway in these patients if possible. Data about levels of PR expression and their association with prognosis in prostatic cancer patients is controversial. Published data in this context were broadly controversial **(Liao et al. 2023)**. The significance of PR in the human prostate and prostate carcinogenesis has not been adequately understood **(Luetjens et al. 2006; Yu et al. 2013; Grindstad et al. 2015)**. The aim of this study was to identify PR status that was assessed by immunohistochemistry and correlation of the receptor status to the patient's overall and progression-free survival.

Materials and Methods

It is a cohort study that was conducted in Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital. It included 50 patients who were diagnosed with metastatic prostate cancer. The patients were registered at our department from February 2020 till April 2021 inclusive. The study included patients presented with a histologically confirmed metastatic prostatic adenocarcinoma from the start. Patients aged ≥18 years with a performance status ≤ 2 as determined by Eastern Cooperative Oncology Group (ECOG) performance status. We excluded non metastatic disease, current or previous history of other malignancy. All patients were diagnosed using basal PSA level, pathological confirmation of the prostate adenocarcinoma with radiological evidence of the metastatic disease using bone scan and CT chest, abdomen with pelvic post-contrast MRI for assessment of the primary disease. PR status in the prostate cancer specimens were evaluated by using IHC. Patient's treatment plan was decided by a panel of clinical oncology consultants and specialists. Patients either received only ADT (bilateral subcapsular orchiectomy or GnRH agonist which included either zoladex either 3.6 mg SC/28 days or 10.8 mg SC/12 weeks with or without casodex 50 mg once daily) or ADT plus taxotere (either 75 mg/m2 every 3 weeks or 50 mg/m2 every 2 weeks) in high volume metastatic disease (defined as at least 4 bone metastases or including at least 1 lesion outside vertebral column or visceral metastasis). Zoledronic acid was prescribed in most of bone metastatic prostate cancer patients with calcium and vitamin D support if was indicated. Palliative radiotherapy was received for symptomatic osteolytic bone metastasis and spinal cord compression. Primary disease radiation therapy (55 Gy over 20 fractions) was received by some patients presented with low volume metastatic disease defined as less than 4 bone metastases without visceral metastasis. Patients were followed up for at least 2 years by serum PSA every 2-3 months. Radiological assessments were evaluated every 6 months by bone scan in bone metastatic patients and post-contrast CT (chest-abdomen-pelvis) in visceral metastatic patients. Biochemical and radiological response to different lines of treatment were assessed at 6 months. We correlated PR status, clinicopathological and treatment data to progression free survival (PFS) and overall survival (OS).

Pathological procedure

Pathological specimens that were preserved in the archive of the Pathology Department of Urology and Nephrology center, Mansoura University, were analyzed. Paraffin-embedded blocks of trans-rectal ultrasound-guided needle prostate biopsy specimens of the patients were prepared using hematoxylin and eosin staining. Tissue sections were cut into a thickness of (4 to 6 μm) and revised to confirm the diagnosis of adenocarcinoma and sufficient tissue for immune-histochemical analysis. Immunohistochemical Staining was performed using ROCH automatic immunohistochemistry instrument model VENTANA BenchMark Ultra autostainer and monoclones, PR: anti-Progesterone Receptor (PR) (IE2) Rabbit Monoclonal Primary Antibody REF 790-2223.Ventana Ultra View DAB detection system was used.

Sample size

It was calculated by using Power Analysis and Sample Size (PASS) Software (version 15, 2017). NCSS, LLC. Kaysville, Utah, USA. Based on previous studies **(Grindstad et al. 2018)**, a two-sided, one-sample logrank test calculated from a sample of 50 subjects achieves 96.3% power at a 0.050 significance level to detect a hazard rate of 0.400 in positive group when the hazard rate of negative group is 0.200. Subjects are accrued for a period of 1.0 year. Follow-up continues for a period of 2.0 years after the last subject is added. The probability that a subject will experience an event during the study is 0.6297. The expected number of events during the study is 31. It is assumed that the survival time distributions of both groups are approximated reasonably well by the Weibull distribution with a shape parameter of 1.00.

Statistical analysis

Data were entered and analyzed using IBM-SPSS software (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.) and MedCalc software (version 18.9.1). Qualitative data were expressed as frequency (N) and percentage (%) and Quantitative data were initially tested for normality using Shapiro-Wilk's test with data being normally distributed if $p>0.050$. The presence of significant outliers was tested for by inspecting the boxplots. Quantitative data were expressed as mean ± standard deviation (SD) if normally distributed or median and interquartile range (IQR) if not. Qualitative data were compared by Chi-Square or Fisher's exact test. Phi was used to test the association for 2X2 crosstabulation. The Kaplan-Meier method was used to estimate the probability of survival past given time points. The survival distributions of two or more groups of a between-subjects factor were compared for equality using log-rank test. Cox regression was used to investigate the effect of several variables upon the time a specified event takes to happen. The hazards ratio associated with a predictor variable is given by the exponent of its coefficient; with a 95% confidence interval. The RMST was reported with its 95% confidence interval at 24-months' time point. Differences of RMST between groups was reported as P-value.

Ethical considerations

The study protocol was submitted for approval by the Institutional Research Board (IRB), Faculty of Medicine, and Mansoura University. Informed written consent was obtained from each participant patient after assuring confidentiality.

Results

Clinico-pathological and treatment data are described in tables (1&2). The mean age at diagnosis was 67.1 ± 7.1 years. Most of the patients (84%) had a Gleason pattern of 4-5. Thirty-eight patients were presented with a high-volume metastatic disease.

Table (1): Clinico-pathological characteristics of the study patients.

Clinico-pathological characteristic	N (%)
Age (years)	
≤ 65 years vs. > 65 years	23 (46%) vs. 27 (54%)
ECOG	
0 vs. 1-2	10 (20%) vs. 40 (80%)
Basal Total PSA (ng/ml)	
<100 vs. ≥100	22 (44%) vs. 28 (56%)
Radiological T stage	
T2 vs. T3-4	5 (10%) vs. 45 (90%)
Radiological N stage	
N0-1 vs. N2-3	42 (84%) vs. 8 (16%)
Biopsy cores number	
≤ 8 vs. > 8	22 (44%) vs. 28 (56%)
+ve biopsied cores	
≤ 50% vs. > 50%	20 (40%) vs. 30 (60%)
Gleason pattern	
1-3 vs. 4-5	8 (16%) vs. 42 (84%)
Metastatic sites	
Bone only vs. Visceral ± bone	38 (76%) vs. 12 (24%)
Disease volume	
Low volume vs. High volume	12 (24%) vs. 38 (76%)
	Mean ± SD
Age (years)	67.1 ± 7.1
	Median (Q1-Q3)
Number of biopsy cores	10 (8 – 12)
Percentage of positive tissue	60 (40 – 70%)

Table (2): Patient treatment and treatment response

Parameter	N (%)
First line treatment	
ADT	33 (66%)
ADT *plus* Taxotere	17 (34%)
Primary disease irradiation	
No	43 (86%)
Yes	7 (14%)
Response at 6-months	
Responsive disease	46 (92%)
Progressive disease	4 (8%)
PSA nadir (ng/ml)	
≤ 4	38 (76%)
> 4	12 (24%)
Time to PSA nadir (months)	
≤ 6	19 (38%)
> 6	31 (62%)
	Median (Q1-Q3)
PSA nadir (ng/ml)	1.3 (0.5 – 4.08)
Time to PSA nadir (months)	9 (6 – 12)

IHC detected positive PR in 48% (24/50) of the cases with 30% (15/50) of the cases showing nuclear staining in ≥ 10% of the tumor cells and 18% (9/50) of the cases experiencing nuclear staining in <10% of the tumor cells (figures1-4).

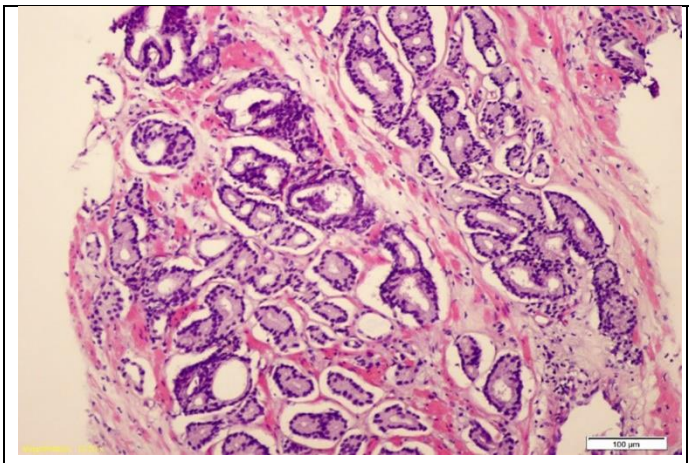

Figure (1): Prostatic adenocarcinoma moderately differentiated showing medium and small glands of irregular size and spacing with ill-defined infiltrating edges. Combined Gleason score 3+4=7. Hx & E x200

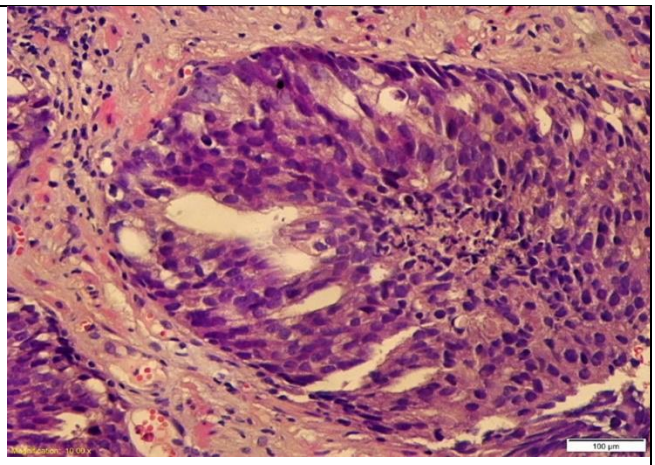

Figure (2): Prostatic adenocarcinoma poorly differentiated showing cribriform sheets with central necrosis comedo like with ill-defined infiltrating edges. Combined Gleason score 5+5=10. Hx&E x200

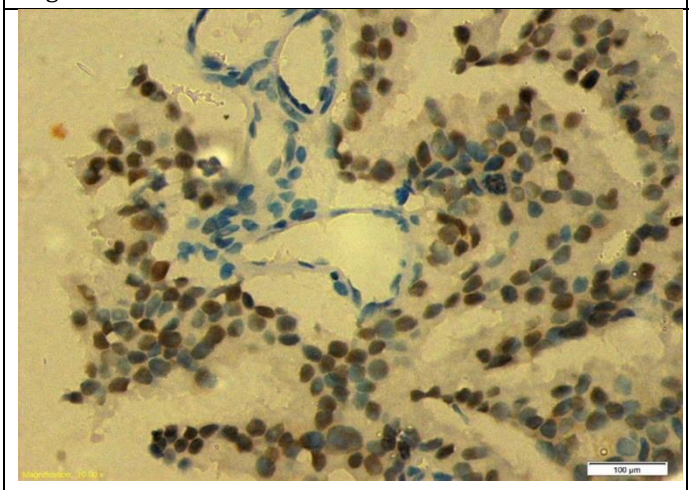

Figure (3): Progesterone receptor showing moderate diffuse nuclear staining involving 70 % of the tumor cells. Immunoperoxidase x400

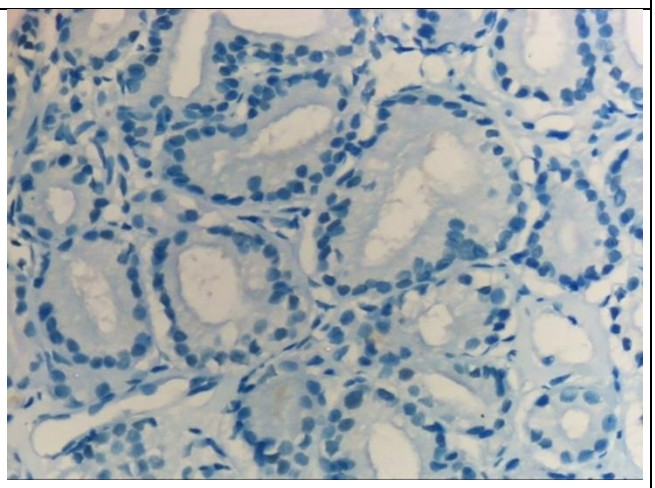

Figure (4): Negative progesterone receptor staining.

Our patients had a median overall survival of 27 months with a range of (22-30 months). The median PFS of our cohort was 20 months with a range of (15-30) months. Cases with PR positive staining had statistically insignificant improved OS and PFS RMST at 24 months (23 months vs. 22 months and 20 months vs. 17 months with P= 0.20 and 0.16 respectively) (figures 5-8 & table 3)

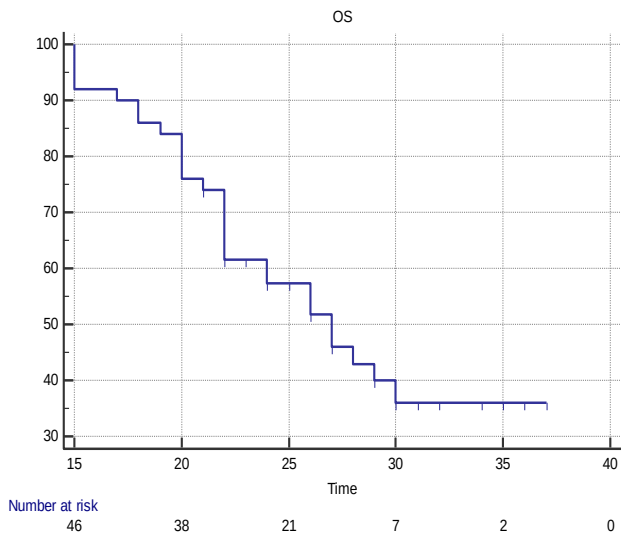

Figure (5): OS of metastatic prostate cancer

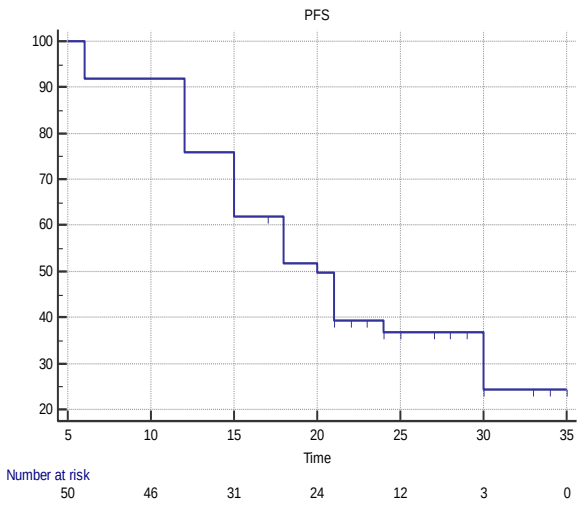

Figure (6): PFS of metastatic prostate caner

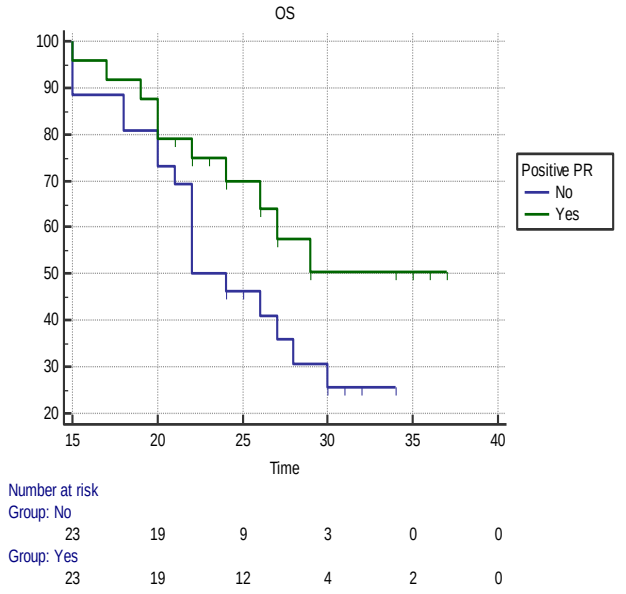

Figure (7): PR status effect on OS

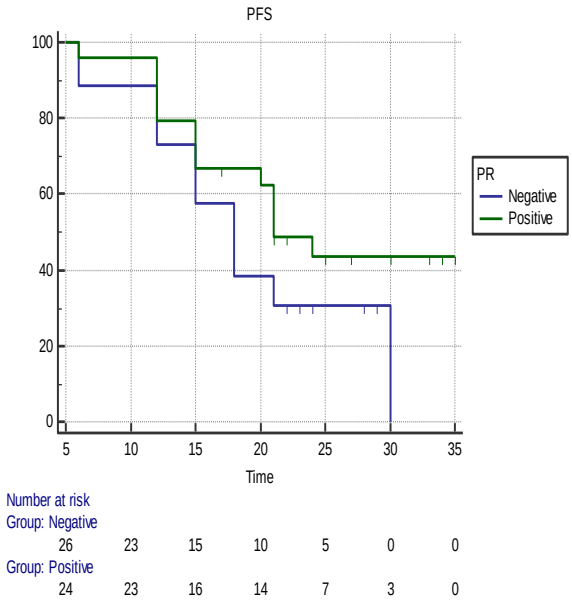

Figure (8): PR status effect on PFS

Table (3) Comparison of OS and PFS according to PR status:

Risk factor	OS n/N (%)	Median OS (months) (95% CI)	Log rank test		RMST at 24- months	
			χ^2	Sig.	RMST (months)	Sig.
PR						
Positive	10/24 (41.7)	-	2.8	.097	21.7 (20.5-22.9)	.20
Negative	18/26 (69.2)	22 (21-28)			22.7 (21.7-23.7)	
Risk factor	**PFS n/N (%)**	**Median PFS (months) (95% CI)**	**Log rank test**		**RMST at 24- months**	
			χ^2	Sig.	RMST (months)	Sig.
PR						
Positive	13/24 (54.2)	21 (15-24)	2.7	.099	19.6 (17.4-21.7)	.16
Negative	20/26 (76.9)	18 (15-21)			17.3 (15-19.6)	

Notes: CI=confidence interval. RMST = restricted mean survival time. (-) = Survival probability didn't reach 50%. χ^2: Chi-square. Sig. = significance (P value)

Table (4) showed that patients with performance status of ECOG 0 had statistically significant better restricted mean survival time (RMST) of about 32 months. Patients with Gleason pattern of four or five, visceral metastasis and a high volume disease had poor OS. Primary disease irradiation, responsive disease at 6 months after 1st line treatment and PSA nadir of ≤ 4 ng/ml were associated with improved OS (P values 0.05, 0.001 and 0.01 respectively) (table 5). Univariate analysis showed that ECOG (0 versus 1-2), local T staging (T3-4 versus T2), disease response at 6 months after 1st line treatment (regressive or stationary versus progressive) and PSA nadir value (≤ 4 ng/ml versus > 4 ng/ml) significantly affected OS. However, multivariate analysis revealed ECOG, local T stage and local disease irradiation were independent prognostic factors affecting OS (table 6).

Table (4): Comparisons of clinicopathological characteristics according to OS.

Risk factor	OS n/N (%)	Median OS – months (95% CI)	Log rank test		RMST at 24- months	
			χ^2	Sig.	RMST	Sig.
Age (Years)						
≤65	12/23 (52.2)	28 (24-29)	1.0	.32	22.6 (21.4-23.7)	.37
>65	16/27 (59.3)	24 (20-30)			21.9 (20.8-22.9)	
ECOG						
0	3/10 (30)	-	4.59	**.032**	31.9 (28.9-34.8)	**.001**
1-2	25/40 (62.5)	26 (22-29)			25.6 (23.3-27.9)	
Basal Total PSA (ng/ml)						
<100	11/22 (50.0)	30 (21-30)	0.3	.57	22.6 (21.7-23.5)	0.32
≥100	17/28 (60.7)	26 (22-29)			21.8 (20.6-23.1)	
Radiological T stage						
T2	5/5 (100)	19 (15-28)	10.2	**.001**	18.8 (15.7-21.9)	**.02**
T3-4	23/45 (51.1)	27 (24-30)			22.6 (21.8-23.3)	
Radiological N stage						
N0-1	24/42 (57.1)	26 (22-30)	0.01	.93	22 (21.1-22.9)	007
N2-3	4/8 (50.0)	27 (20-28)			23.2 (22.2-24.2)	
+ve biopsied cores						
≤ 50%	10/20 (50)	27 (20-27)	0.1	0.71	21.6 (20.2-23)	.26
> 50%	18/30 (60)	26 (22-30)			22.6 (21.7-23.4)	
Gleason pattern						
1-3	2/8 (25.00)	-	3.59	**.05**	23.4 (22.6-24.2)	**.02**
4-5	26/42 (61.90)	26 (22-29)			22 (21.0-22.9)	
Metastatic sites						
Bone only	19/38 (50.00)	28 (22-30)	1.55	.21	22.3 (21.4-23.2)	.62
Visceral ± bone	9/12 (75.00)	22 (19-29)			21.8 (20.3-23.4)	
Disease volume						
Low volume	3/12 (25.0)	-	4.1	**.04**	23.3 (22.2-24.3)	**.05**
High volume	25/38 (65.8)	26 (22-29)			21.8 (20.9-22.8)	

Notes: CI=confidence interval. RMST = restricted mean survival time. (-) = Survival probability didn't reach 50%. χ^2: Chi-square. Sig. = significance (P value)

Table (5): Median OS according to treatment lines and PSA nadir.

Risk factor	OS n/N (%)	Median OS – months (95% CI)	Log rank test		RMST at 24- months	
			χ^2	Sig.	RMST	Sig.
First line treatment						
ADT	18/33 (54.55)	27 (22-30)	0.37	.54	22.21 (21.24-23.18)	.89
ADT+Taxotere	10/17 (58.82)	26 (20-28)			22.09 (20.76-23.42)	
Primary disease irradiation			3.9	**.05**		**.01**
Yes	1/7 (14.29)	-			23.6 (22.8-24.4)	
No	27/43 (62.79)	26 (22-29)			21.94 (21.1-22.8)	
Response at 6 months			11.1	**.001**		.07
Responsive	24/46 (52.2)	28 (24-30)			21.1 (20.6-21.7)	
Progressive	4/4 (100)	18 (15-22)			18.8 (16.2-21.3)	
PSA nadir (ng/ml)						
≤ 4	17/38 (44.8)	29 (24-29)	7.6	**.01**	22.5 (21.6-23.4)	.12
> 4	11/12 (91.7)	22 (19-26)			21.2 (19.8-22.6)	
Time to PSA nadir (months)			1.4	.23		**.02**
> 6	16/31 (51.6)	27 (24-29)			22 (22.2-23.7)	
≤ 6	12/19 (63.2)	22 (18-30)			20.9 (19.4-22.4)	

Notes: CI=confidence interval. RMST = restricted mean survival time. (-) = Survival probability didn't reach 50%. χ^2: Chi-square. Sig. = significance (P value)

Table (6): Risk factors affecting OS

Risk factor	Univariate			Multivariate		
	Crude HR	95% CI	Sig.	Adjusted HR	95% CI	Sig.
ECOG						
PS 0	r(1)	r(1)	**.050**	r(1)	r(1)	**.015**
PS 1-2	3.3	1-11.1		7.02	1.5-33.5	
Local radiologic 'T' stage						
T3-4	r(1)	r(1)	**.004**	r(1)	r(1)	**< .001**
T2	4.2	1.6-11.4		11.1	3.1-39.7	
Gleason pattern						
1-3	r(1)	r(1)	.085	r(1)	r(1)	.970
4-5	3.6	0.84-15.1		1.03	0.2-5.7	
Disease volume						
Low	r(1)	r(1)	.063	r(1)	r(1)	.292
High	3.1	0.94-10.4		0.4	0.1-2.1	
Local disease irradiation						
Received	r(1)	r(1)	.091	r(1)	r(1)	**.049**
Not received	5.6	0.76-41.2		17.2	1 -292.2	
Response at 6-months						
Responsive	r(1)	r(1)	**.004**	r(1)	r(1)	.089
Progressive	5.2	1.7-16.1		2.8	0.9-9.2	
PSA nadir						
≤4 ng/ml	r(1)	r(1)	**.010**	r(1)	r(1)	.485
>4 ng/ml	2.7	1.3-5.9		1.4	0.6-3.3	
PR status						
Positive	r(1)	r(1)	.114	r(1)	r(1)	.565
Negative	1.9	0.86-4.1		1.3	0.5-3.1	

This table shows the results of cox proportional hazards regression, which was run to ascertain the effects of ECOG, local radiological T stage, Gleason pattern, disease volume, primary disease irradiation, disease response at 6 months, PSA nadir and molecular subtype on OS. Model (1) was statistically significant ($\chi 2$ [8] = 29.6, p-value <.001) and C-index with its 95% CI was 0.851 (0.722-0.936).

Our study showed that good performance status improved median PFS (P= 0.03). Early local disease stage, Gleason patterns 4 and 5 and a high-volume metastatic disease displayed a poor median PFS (P=.003, 0.02 and 0.05) (table 7). Primary disease irradiation and PSA nadir ≤4 ng/ml were associated with significantly better median PFS (P=0.05 and 0.001, respectively) (table 8). Univariate analysis showed that local T staging (T3-4 versus T2) and PSA nadir value (≤ 4 ng/ml versus > 4 ng/ml) significantly affected PFS (P= 0.01 and .004, respectively). However, multivariate analysis revealed that local disease irradiation was independent prognostic factors affecting PFS with P=0.001(table 9).

Table (7): Comparisons of clinicopathological characteristics according to PFS.

Risk factor	PFS n/N (%)	Median PFS (months) (95% CI)	Log rank test		RMST at 24- months	
			χ^2	Sig.	RMST- months	Sig.
Age (Years)						
≤65	15/23 (65.2)	21 (15-30)	0.6	.43	19.6 (17.7-21.4)	015
>65	18/27 (66.7)	18 (12-24)			17.3 (14.9-19.8)	
ECOG						
0	4/10 (40)	-	4.7	**.03**	22.4 (21.1-23.7)	**<.001**
1-2	29/40 (72.5)	18 (15-21)			17.4 (15.5-19.2)	
Basal Total PSA (ng/ml)						
<100	13/22 (59.1)	21 (15-21)	0.6	.45	19.1(16.7-21.4)	.46
≥100	20/28 (71.4)	18 (12-30)			17.8 (15.7-20)	
Radiological T stage						
T2	5/5 (100)	12 (6-18)	8.7	**.003**	12.6 (9.1-16.1)	.07
T3-4	28/45 (62.2)	21 (18-30)			16 (15-17)	
Radiological N stage						
N0-1	28/42 (66.67)	21 (15-30)	0.23	.63	17.8 (16.3-19.2)	.59
N2-3	5/8 (62.5)	18 (6-20)			16.5 (12.1-20.9)	
+ve biopsied cores						
≤ 50%	12/20 (60)	18 (12-30)	0.1	.83	17 (15.2-20.7)	.69
> 50%	21/30 (70)	21 (15-24)			18.6 (16.7-20.6)	
Gleason pattern						
1-3	2/8 (25)	-	5	**.02**	22.1 (19.8-24.4)	.003
4-5	31/42 (73.81)	18 (15-21)			17.7 (15.9-19.4)	
Metastatic sites						
Bone only	24/38 (63.2)	21 (15-30)	0.9	.35	18.8 (16.9-20.7)	.32
Visceral ± bone	9/12 (75)	15(12-21)			17 (13 -20.1)	
Disease volume						
Low volume	5/12 (41.7)	-	3.9	**.05**	21.4 (19.2-23.6)	.007
High volume	28/38 (73.7)	18 (15-21)			17.4 (15.5-19.3)	

Notes: CI=confidence interval. RMST = restricted mean survival time. (-) = Survival probability didn't reach 50%. χ^2: Chi-square. Sig. = significance (P value)

Table (8): Median PFS according to treatment lines and PSA nadir:

Risk factor	PFS n/N (%)	Median PFS (months) (95% CI)	Log rank test		RMST at 24- months	
			χ^2	Sig.	RMST (months)	Sig.
First line treatment						
ADT	22/33 (66.7)	21 (15-30)	0.2	.69	18.9 (17.1-20.7)	.41
ADT+Taxotere	11/17 (64.7)	18 (12-30)			17.4 (14.2-20.5)	
Primary disease irradiation						
Yes	2/7 (28.6)	-	3.7	**.05**	22.1 (19.8-24.5)	**.003**
No	31/43 (72.1)	18 (15-21)			17.8 (16-19.5)	
PSA nadir (ng/ml)						
≤ 4	21/38 (55.3)	21 (18-30)	10.7	**.001**	19.6 (17.9-21.3)	**.003**
> 4	12/12 (100)	15 (6-18)			14.5 (11.6-17.4)	
Time to PSA nadir (months)						
> 6	21/31 (67.7)	21 (15-30)	0.23	.63	19.6 (17-21.1)	.08
≤ 6	12/19 (63.2)	18 (12-21)			16.4 (13.3-19.6)	

Notes: CI=confidence interval. RMST = restricted mean survival time. (-) = Survival probability didn't reach 50%. χ^2: Chi-square. Sig. = significance (P value)

Table (9): Univariate and multivariate analysis of risk factors affecting PFS.

Risk factor	Univariate			Multivariate		
	Crude HR	95% CI	Sig.	Adjusted HR	95% CI	Sig.
ECOG						
PS 0	r(1)	r(1)	**.053**	r(1)	r(1)	.083
PS 1-2	2.8	1-8.1		2.96	0.9-10.1	
Local radiologic 'T' stage						
T3-4	r(1)	r(1)	**.010**	r(1)	r(1)	**.001**
T2	3.7	1.4-10		6.1	2-18.7	
Gleason pattern						
1-3	r(1)	r(1)	.054	r(1)	r(1)	.287
4-5	4.1	1-17.1		2.4	0.5-11.3	
Disease volume						
Low	r(1)	r(1)	.076	r(1)	r(1)	.411
High	2.4	0.9-6.2		0.6	0.2-2.2	
Local disease irradiation						
Received	r(1)	r(1)	.092	r(1)	r(1)	.116
Not received	3.4	0.8-14.3		5.1	0.7-38.5	
PSA nadir						
≤4 ng/ml	r(1)	r(1)	**.004**	r(1)	r(1)	.181
>4 ng/ml	2.9	1.4-6		1.8	0.8-4.1	
PR status					-	
Positive	r(1)	r(1)	.130	r(1)	r(1)	.392
Negative	1.7	0.9-3.5		1.4	0.6-3.2	

Overall model fit show cox proportional hazards regression which was run to ascertain the effects of ECOG, local radiological T stage, Gleason pattern, disease volume, primary disease irradiation, PSA nadir and PR status

on PFS. The model was (1) statistically significant. (χ2 [7] = 23.12, p-value 0.0016), C-index (95% CI) = 0.878 (0.754-0.953).

Discussion

Data about level PR expression and its association with prognosis in prostatic cancer patients is controversial. Published data in this context were broadly divided into two periods. The first was the period between 2003 and 2015 with high rate of research that increased yearly and the second was between 2016 and 2021 when the number of published data gradually decreased. PR status has been suggested by numerous researchers to become possible novel treatment strategy for prostate cancer **(Liao et al. 2023)**.

Our study aimed at studying the prognostic value of the progesterone receptor status in 50 patients presented with de novo metastatic prostate cancer. Patients' mean age at diagnosis was 67.1 ± 7.1 years which was similar to that reported in a study to evaluate the immunoexpression of ER and PR in 13 cases with prostatic adenocarcinoma and documented a mean age of 67.38 ± 0 7.74 years **(Bera et al. 2020)**. Naskar and his colleagues studied PR expression in 50 radical prostatectomy specimens (34 cases were diagnosed as nodular hyperplasia (68%), 12 cases as prostatic adenocarcinoma (24%) and 4 cases as prostatic intraepithelial neoplasia (8%)) and reported a mean age of 68.66 years **(Naskar et al. 2014)**. Most of the patients (84%) had a Gleason pattern of 4-5 that was similar to that was reported in a study that was performed in de novo metastatic prostate cancer with most of the patients had a Gleason pattern of 4-5 (44/53 patients) **(Vandekerkhove et al. 2019)**. Additionally, 75% of the adenocarcinoma cases in the study performed by Naskar and his colleagues showed higher Gleason scores between 8 and 10 **(Naskar et al. 2014)**.

The most common metastatic site was bone with visceral metastasis in only 24% of the patients which was similar to that was reported by Finianos and his colleagues when performed a study to characterize the differences between prostate cancer patients presenting with de novo versus primary progressive metastatic disease and declared that bone was the most common metastatic site **(Finianos et al. 2018)**.

Our study showed PR positive staining in the tumor cells of 24 patients (48%) with 9 (18%) patients having low staining and 15 (30%) with high staining. This is nearly similar to the report by **Bera et al. (2020)**, **Naskar et al. (2014)** and **Bonkhoff et al. (2001)** who declared positive PR staining in 38.5% (33% (4/12) and 41% (17/41) of their study patients, respectively. However, Kang et al.1998 had shown positive PR expression in 93.3% of the cases. Another study reported absence of the PR staining in prostatic adenocarcinoma cells **(Kaur et al. 2021)**.

Grindstad et al. (2015) who conducted a study to evaluate the level of PR expression in 535 patients who underwent radical prostatectomy for prostatic adenocarcinoma, reported that PR expression was evident in 85% of their patients. Many other studies also confirmed PR positivity in some prostatic adenocarcinoma cells as **Latil et al. (2000)** and **Hiramatsu et al. (1996)**. Other studies reported the absence of PR expression in tumor cells as **Yu et al. (2013)**.

This discrepancy may be explained by different numbers of tissue samples, different tissue processing or different antigen retrieval methods and different antibodies used with a lack of methodological standardization.

Although it has not achieved statistical significance, positive PR expression in the current study is associated with a slight improvement in OS and PFS versus negative expression. On univariate and multivariate analysis, PR expression couldn't be considered to have any significant prognostic value. This is different to what was reported by **Grindstad et al. (2015)** who documented PR positivity as an independent prognostic factor for progression and clinical failure in prostate cancer. This discrepancy can be explained by different patient categories (non-metastatic disease).

Hou et al. (2022) demonstrated that progesterone is considered an oncogenic hormone in patients with prostate cancer and suggested that a large benefit can be achieved in these patients by the elimination of its oncogenic effects. As our study reported positive PR status in more than 45% of the patients, we suggest driving a wider clinical trial to study PR status in metastatic prostate cancer cells that might consider anti-progesterone receptor drugs as a new treatment strategy in these patients.

Cases with good performance status (ECOG 0) had statistically significant better OS and PFS and were considered to be a prognostic factor for OS on univariate and multivariate analyses. Also, cases presented with visceral metastasis had worse OS and PFS compared to those with only bony metastasis. However, Cox proportional-hazards regression didn't show a statistically significant association with PFS or OS.

Multiple studies provided data on the association of ECOG with OS in metastatic prostate cancer patients and revealed worse OS in patients with poor performance status. Also, data revealed that visceral metastasis is associated with worse OS **(Yanagisawa et al. 2023)**

Ten percent (10%) of our study cases presented with early primary disease T2 (5 cases) which is nearly similar to the study cohort by Parker and his colleagues **(Parker, Chris C. et al. 2022)** where 9% of their patients had presented with primary T2 disease. OS and PFS were statistically worse in patients with T2 primary disease in comparison to those with more locally advanced disease. On univariate and multivariate analyses, early primary disease is considered as an independent prognostic factor for poor survival. A metastatic carcinoma despite early primary disease with absent or mild local disease symptoms may point to aggressive biological behavior of the underlying disease.

Cases with higher Gleason patterns (4-5) in our study demonstrated statistically significant worse median OS (26 months) and PFS (18 months). Multiple studies have documented that Gleason pattern 5 was associated with aggressive prostate cancer. **Kryvenko et al. (2020)** reported increased risk of metastasis and death with Gleason pattern 5. **Tsao et al. (2015)** documented that patients presented with GS 9–10 showed a higher risk of metastasis and death. A recent study also demonstrated that univariate and multivariate analyses identified Gleason pattern 5 as a poor prognostic factor for OS **(Nakagawa et al. 2022)**.

The addition of primary disease irradiation was also associated with better OS and PFS and was considered an independent prognostic factor for OS on multivariate analysis. STAMPEDE trial reported improved failure-free survival with primary disease irradiation **(Parker, C. C. et al. 2018)**.

Conclusion

PR expression status might be associated with metastatic prostate cancer prognosis. However, further work should be strongly considered to verify the obtained data on a larger sample size so that it would be possible to evaluate the correlation of PR expression with different clinic-pathological characteristics and treatment responses to various available lines of treatments.

Study limitations

Our study may have some limitations. First, we evaluated PR status using ROCH automatic immunohistochemistry instrument model VENTANA BenchMark Ultra autostainer and monoclones. Although this method is well-established and standardized for immunohistochemistry in breast cancer, there is no standardized method for IHC evaluation in prostate cancer. Second, our primary endpoint was prostate cancer classification according to the receptor status, we recommend a new study with cohort stratification based on disease volume and treatment used with better determination of the role of the different therapeutic strategies in different receptor expressions. Last, a larger sample size should be considered.

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