# Retrospective analysis of prognostic factors, management, and pattern of failure in Metastatic Prostatic Cancer in Assiut University Hospital in the last ten years

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## Abstract:

**Background**: Prostate cancer (PC) is the fourth most prevalent cancer among men in Egypt accounting for 3.5% of new cancer cases and 2.5 % of male cancer deaths; the metastatic disease affects 6% of new PC cases, with a 5-year survival rate of 29%. Because metastatic PC is less curable, its treatment options and outcomes are particularly important.

**Aim of work**: To evaluate the Patients' characteristics, prognostic factors, therapeutic modalities, treatment outcomes and failure pattern of metastatic prostatic cancer patients in Assiut University Hospital since 1/1/2009 to 1/1/2019.

**Patients and methods:** During the study period (2009-2019); data from 111 patients with metastatic prostatic cancer in Assiut University Hospital was analyzed.

**Results:** Mean age of patients is 71 years; performance status (PS) 2 was the most represented PS (59%). Fifty five percent of patients were non-smokers. About comorbidities, 30% of the patients had other systemic disorders. Urinary symptoms were the most common manifestations (72%). Prostatic adenocarcinoma was the most prevalent pathology. The most frequent Gleason score (GS) was GS 7 (30%). After androgen deprivation therapy (ADT); 58% of patients had stable disease. While progression occurred in 41%, with a median progression-free survival (PFS) of 11 months. Of those who progressed post castration 22% were treated with chemotherapy, with median PFS of 8 months. 70% of patients received palliative bone radiotherapy. The median overall survival (OS) of all cases was (66 months).

Regarding prognostic factors: combined ADT had significantly improved median overall survival (68 months) than single drug (65 months). Patients with castrate resistant prostate cancer (CRPC) had significantly lower survival; reducing the chance of survival by 4.065 times. Performance status had no significant effect on survival.

**Conclusion:** Our study on metastatic prostatic patients in Assiut university hospital as a model of patients in developing countries, has presented information about patient characteristics, some prognostic factors, treatment modalities and pattern of failure, showing that ADT was a successful first-line treatment with OS and PFS comparable to those in advanced nations. Combined hormonal treatment seems to be more effective than single therapy, while the diagnosis of CRPC worsens dis ease's outcome.

**Keywords**: metastatic cancer prostate, patient characteristics, prognostic factors, management, pattern of failure.

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## Introduction:

In Egypt, prostate cancer (PC) is the fourth most prevalent cancer among men, accounting for 3.5% of new cancer cases and 2.5 % of male cancer deaths. Prostate cancer has been more common in developed countries. One explanation for these differences in incidence rates is differences in the utility and availability of diagnostic methods, such as the prostatic specific antigen (PSA) test [1].

The metastatic disease affects around 6% of new PC cases, with a 5-year survival rate of only 29%. The poor prognosis of metastatic PC is magnified by the fact that it frequently becomes androgen-independent. Because metastatic PC is less curable, the incidence of this illness is of particular importance [2].

People with the locally progressed disease may experience obstructive or irritative symptoms. In the metastatic stage of prostate cancer, cancer frequently spreads to the bone, causing bone pain [3].

Treatment options for metastatic prostate cancer include androgen deprivation therapy, palliative radiotherapy, chemotherapy and supportive care. Prostate radical radiotherapy improves survival, particularly in low-volume metastatic disease (1–3 skeletal lesions without visceral metastases). Symptomatic disease progression may indicate palliative surgery; this is less common when treated with radical surgery than systemic therapy alone [4].

The majority of metastatic prostate cancer patients responded to androgen restriction therapy at first, but after a year, a high proportion had advanced to castration-resistant prostate cancer [5].

Treatment of castration-resistant CRPC includes sipuleucel-T, abiraterone acetate plus prednisone (AA/P), or chemotherapy with docetaxel 75 mg/m² every three weeks [6]. Docetaxel plus prednisone was approved and used in the treatment protocols after trials with docetaxel revealed a survival advantage in patients with mCRPC [7]. Cabazitaxel, Enzalutamide, and radium-223 are available for second-line treatment of CRPC following docetaxel [6].

This work aimed to determine the pathology, patients' characteristics, prognostic factors, different therapeutic modalities, treatment outcomes, and failing pattern of metastatic prostatic cancer in Assiut University Hospital prostate cancer patients during ten years.

## Patients and Methods:

A retrospective study of data of the patients presented to the clinical oncology department at Assiut University Hospital from 2009 to 2019 with metastatic cancer prostate resulted in 111 patients.

All patient data were evaluated for history, examination, PSA, testosterone levels, pathology, Gleason score, and follow-up imaging; CT, MRI, bone scan, or PET CT to determine the primary disease, type of metastasis, and disease volume.

Various treatment modalities were reviewed: (Surgical castration -bilateral orchiectomy-, hormonal therapy, Chemotherapy, and Radiation therapy). Each treatment line's response, progression-free survival, and overall survival were documented.

*Statistical Analysis:*

Data was collected and analyzed by using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Quantitative data were expressed as mean ± standard deviation (SD) and compared with Student t test. Nominal data were given as number (n) and percentage (%). Chi2 test was implemented on such data. Survival analysis was performed by Kaplan Meier curve. Level of confidence was kept at 95% and hence, P value was considered significant if < 0.05.

## Results:

The Mean age of our patients was 71 years (SD± 8.055), most of patients; 48 patients (43%) were diagnosed at age ranged from 64 to 73 years, 33 patients (30%) were diagnosed at age ranged from 74 to 83 years, 23 patients (20.7%) at age 54 to 63 years, while only 7 patients (6.3%) were at age 84 to 93 years.

The most common ECOG performance status (PS) among the patients at the presentation time was PS 2 represented in 66 patients (59.5%), then PS 3 in 32 patients (28.8%), less likely was PS 1 in 13 patients (11.7%). Considering smoking status among cases of this study; Non-smokers were more than smokers; 61 patients (55%) were non-smokers vs. 50 patients (45%) were smokers.

Table 1: Patient characteristics among enrolled 111 mPC patients

| | **No. (n= 111)** | **%** |
|---|---|---|
| **Age:** | | |
| 54-63 | 23 | 20.7 |
| 64-73 | 48 | 43.20 |
| 74-83 | 33 | 29.70 |
| 84-93 | 7 | 6.30 |
| Mean ± SD (Range) | 71.0 ± 8.055 (53.0 - 92.0) | |
| **Performance status:** | | |
| PS 1 | 13 | 11.7 |
| PS 2 | 66 | 59.5 |
| PS 3 | 32 | 28.8 |
| **Smoking status:** | | |
| Smokers | 50 | 45 |
| Nonsmokers | 61 | 55 |

The most common presenting symptoms were urinary symptoms in 80 patients (72%) collectively; (urine retention, anuria, oliguria in 27%, burning, difficult micturition, dysuria in 21.6%, hematuria in 13.5%, urgency, frequency in 6.3% and incontinence in 3.6%) then bone pain in 26 cases (23.4%), while incidental prostatic enlargement and abdominal pain each was in 2 patients (1.8%) and paraplegia in 1 patient (0.9%). Fig (1).

In terms of comorbidities, about 33of the patients in this study (30%) had other systemic disorders, and of these; Hypertension and diabetes mellitus were the most common chronic disorders discovered in 22 patients (19.8%). Fig (2).

Prostatic adenocarcinoma was the most prevalent pathology in 106 patients (96%) of cases, other pathologies (urothelial carcinoma, neuroendocrine carcinoma and adenosquamous carcinoma) were very low; represented in 2 patients (1.8%), 2 patients (1.8%) and 1 patient (0.9%) respectively. GS 7 was the most overall Gleason score represented in 33 (29.7%) of patients, followed by GS 6 in 23 patients (20.7%). Median PSA level at diagnosis was ≥400ng/ml; the range of PSA level at diagnosis is shown in Table 2.

Table 2: The Range of PSA level of enrolled 111 mPC patients at diagnosis

| | PSA level | Total number | Percentage |
|---|---|---|---|
| Initial PSA | <100 ng/ml | 46 | 41.44% |
| | ≥100<200 ng/ml | 31 | 27.92% |
| | ≥200<300 ng/ml | 10 | 9.01% |
| | ≥300<400 ng/ml | 6 | 5.41% |
| | ≥400 ng /ml | 18 | 16.22% |

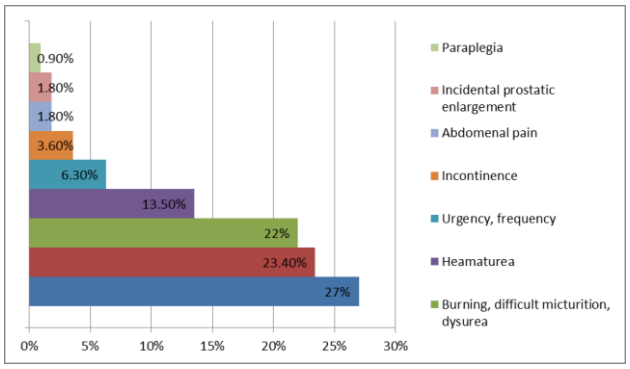


Figure 1: Presenting Symptoms among 111 patients with metastatic prostate cancer enrolled in the study

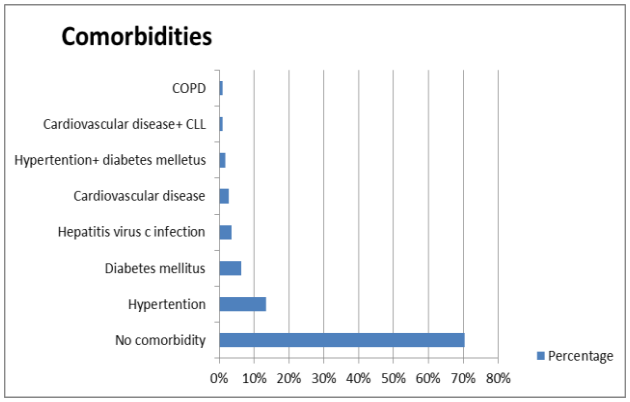


Figure 2: Comorbidities among 111 patients with metastatic prostate cancer enrolled in the study. COPD: chronic obstructive pulmonary disease, CLL: chronic lymphatic leukemia

Most patients had high volume disease (presence of visceral metastasis or ≥4 bone metastases with ≥1 beyond the vertebral bodies and pelvis):72 (65 %) of patients, while 39 (35%) had low volume disease (1–3 skeletal lesions without visceral metastases) Fig (3). The most common site of metastasis was the bone in 104 patients (93.6 %).

All of the patients were given androgen deprivation therapy: Radical orchiectomy with Bicalutamide in 54 (48.6%) of patients, Radical orchiectomy combined with Cyproterone acetate in 8 (7.2%) of patients, Radical orchiectomy alone in 2 (1.9%) of patients, Goserline in 9 (8.1%), Combined Goserline, and Bicalutamide in 38 (34.2%). Response to hormonal treatment among patients; The disease was stable in 64 patients (58%), while 46 patients (41%) showed disease progression and were considered CRPC based on testosterone level, while one patient (1%) was missed. Median progression-free survival after hormone deprivation was (11 months, 95% CI = 9-16) Fig (4). The median overall survival was (66 months, 95% CI = 65-67).

Of CRPC patients; 24 patients (22%) were given (Docetaxel with Prednisone) chemotherapy; 22 (92%) of them exhibited disease progression, while the remaining patients (8%) were stable. After chemotherapy, the median progression-free survival among enrolled patients was 8 months (95% CI= 7-11) Fig (5). The response to chemotherapy seemed to be more pronounced in high volume disease than low volume disease, but the difference is not statistically significant.

Regarding prognostic factors affecting patient's survival: Patients who received maximum (combined) androgen deprivation therapy had a significantly greater median overall survival; 68 months (95% CI = 66-88) than those who received a single drug; 65 months (95% CI = 64-67). (P< 0.001) Fig (6). Patients with CRPC had significantly lower survival; the chance of survival declined by 4.065 times with the diagnosis of CRPC. (Table 3).

Table 3: Survival Outcomes in Patients with mCRPC

| Variable | Beta coefficient | Significance | Effect on Survival Chance |
|---|---|---|---|
| CRPC | -1.402 | 0.001 | -4.065 |

Performance status had no significant effect on survival; patients with PS 1 had median OS was 67 months (95%CI= 65-69), patients with PS 2 median OS was 66 months (95%CI= 65-67) while patients with PS 3 median survival was 65 months. Fig (7)

Seventy eight (70%) of our patients received palliative bone radiotherapy, mostly used dose fraction 30 Gray/ 10 fractions (44 patients; 40%), then 20 gray/5 fractions in 24 (30%) of patients, both doses had the same effect on the palliation of pain.

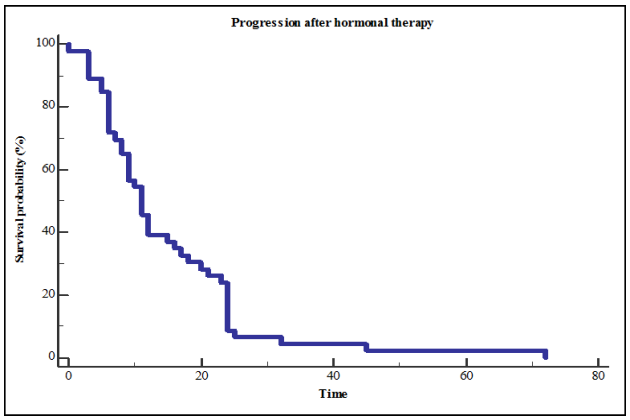


Figure 3: Kaplan-Meier Curve for PFS after Hormonal Therapy. Median PFS among enrolled 111 mPC patients after hormonal deprivation therapy was 11 months (95%CI= 9-16).
PFS: progression free survival, mPC: metastatic prostate cancer

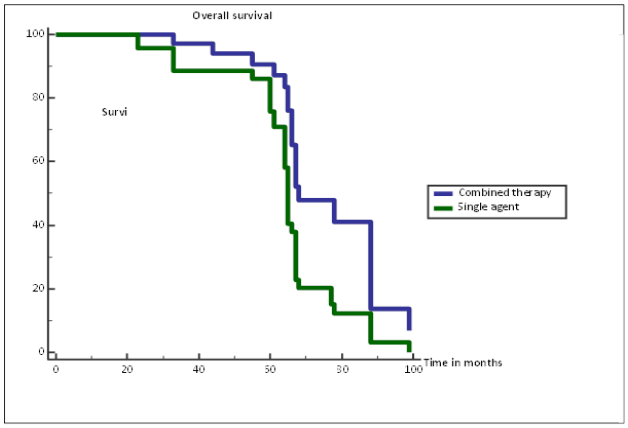


Figure 4: Kaplan-Meier Curve for OS in patients with mPC who recieved combined ADT (median OS:68 month (95%CI= 66-88) vs those who recieved single agent (median OS: 65 month (95%CI=64-67)) (P< 0.001)
OS: overall survival, mPC: metastatic prostate cancer, ADT: androgen deprivation therapy

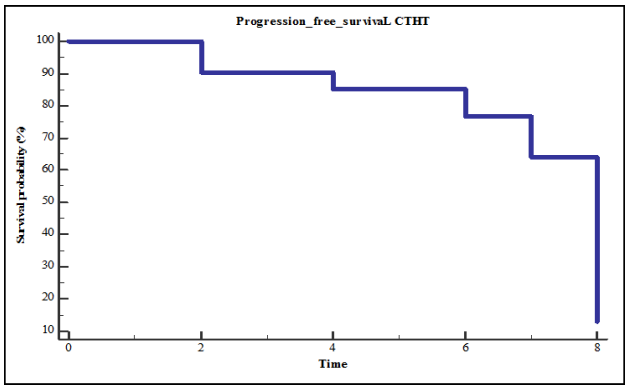


Figure 5: Kaplan-Meier Curve for PFS after Chemotherapy: median PFS among 24 patients received chemotherapy was 8 months (95%CI= 7-11)
PFS: Progression free survival

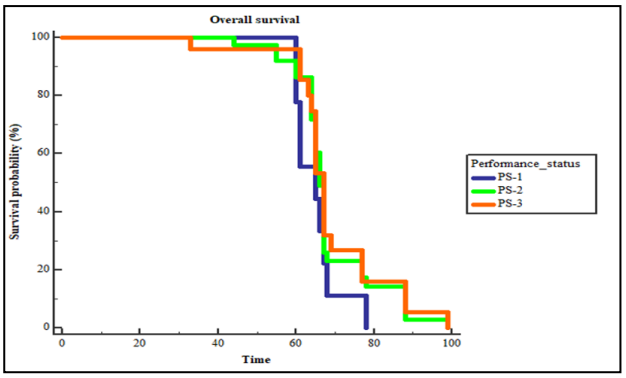


Figure 6: Overall survival of patients based on the performance status. PS of the enrolled 111 mPC patients had no significant effect on the overall survival (P= 0.36). Patients with PS-1 had median OS was 67 months (95%CI= 65-69), patients with PS-2 had median OS was 66 months (95%CI= 65-67) while patients with PS-3 had median survival was 65 months (61-66).
PS: performance status, OS: overall survival, mPC: metastatic prostate cancer.

## Discussion:

In this study; All metastatic prostate patients in Assiut university hospital were retrospectively reviewed for patient characteristics, presenting symptoms, accompanying chronic conditions, pathology, Gleason score, metastatic details, prognostic factors, therapeutic approaches, and response to therapy.

The total number of cases was 111; we found that the mean age of our patients was 71 years old, with the majority of cases falling within the age group of 63 to 83 years old, corresponding to the age of patients in developed countries, where the most prevalent age is ≥65 years old and uncommon ≤50 years old [8]. With a median age of 70 years, most studies agreed with the findings [9, 10].

Smokers among patients in this study were less than nonsmokers (45% VS 55%). This finding agrees with Jimenez Mendoza et al, who discovered that smokers have a reduced risk of PC than nonsmokers, which they explained by an increase in smoking cessation once PC or another chronic condition was detected [11].

Most epidemiological research has found no link between smoking and prostate cancer, although specific studies have discovered that heavy smokers had a 2-3 times increased risk of prostate cancer [12].

We found that 30% of patients had other chronic diseases, and of these; Hypertension and diabetes mellitus were the most common chronic disorders discovered. The study agreed with this result provided prevalence of comorbid conditions in prostate cancer patients was (30.5%) [13], while in the United States, 54% of patients with prostate cancer had a preexisting chronic condition, of which the most prevalent were cardiometabolic and respiratory chronic conditions [10].

The most common presenting symptoms among our patients were urinary tract complaints in 72% of cases, then bone pain in 23% of cases. Similarly, in another study, most patients had urologic complaints [14]. While in a study in Spain, a low percentage of patients

presented with urinary tract complaints or bone pain, the high percentage of cases diagnosed in the early stages of the disease in the developed countries can explain this [15].

In this analysis, the most common pathology was prostatic adenocarcinoma (95.5%), which is consistent with global prostate cancer patient characteristics, with prostatic adenocarcinoma accounting for 93.75% of cases [16].

The majority of patients in this study had high volume metastasis (65%), with bone metastasis accounting for the most of metastasis (73%) of patients, which is consistent with that reported in a population-based analysis by Gandalia et al 2014 [17]. While only 31% of patients in another study had initial metastatic dissemination in the bones. [18].

All of the patients were given androgen deprivation therapy consisted of; surgical castration (bilateral orchiectomy) combined with Bicalutamide in 48.6% of patients, Combined Goserline and Bicalutamide in 34.2%, the remaining received surgical castration combined with Cyproterone acetate in 7.2% of patients, surgical castration alone in 1.9% of patients, Goserline in 8.1%. Regarding the response to hormonal treatment among patients in the study group, in 58% of patients, the disease was stable, while in 41% disease progressed and was diagnosed to have CRPC by assessment of testosterone level.

Patients who received androgen deprivation therapy had a median Progression-free survival (PFS) of 11 months, nearly the same as that reported by Fizazi et al 2017 [5]. However, it is still lower than the result published by Sharifi et al in 2005 [19].

The median overall survival in our study was 66 months (95% CI = 65-67). Global OS data from several trials are comparable to our results for ADT alone, with OS ranging from 54 to 71 months [20-22]. In our study, patients who received combined hormonal therapy had a significantly greater median overall survival (68 months, 95% CI = 66-88) than those who received a single agent (65 months, 95% CI = 64-67) ($P<0.001$), similarly, Akaza et al also reported that combination androgen therapy had a significant overall survival advantage over hormonal monotherapy [23]. In our study, survival is significantly adversely affected in CRPC. The occurring of castrate resistance decreased survival chance by 4.065; this is comparable to the finding of a systematic review that confirmed the poor survival associated with CRPC [24].

Cytotoxic chemotherapy and androgen targeted therapies are the two main lines of therapy for mCRPC. Docetaxel and prednisone are the recommended first-line chemotherapy for mCRPC. [22,25]. Patients who progressed to CRPC In this study (24 patients) received chemotherapy treatment in the form of a combination of (Docetaxel/prednisolone) which was the available treatment in Assiut university hospital.

Median progression-free survival after chemotherapy was (8 months, 95% CI = 7.7-11); this result is consistent with the result reported by Kawahara. [25], However, in another study, PFS after Docetaxel and Prednisone was 6.1 months [26].

In 2017 Consensus Conference on Advanced Prostate Cancer, most experts (90%) agreed that docetaxel would be the best option in patients with mCRPC who showed progression after AR-targeted therapy. Cabazitaxel would be preferred In patients progressed after docetaxel, based on the CARD trial, as Cabazitaxel improved both PFS and OS compared to AR-targeted therapy in patients previously received docetaxel [27], as Cabizataxel was not available at the time of the study, so only docetaxel and continuous ADT were used.

*Limitations:*

Retrospective nature of this work, our study comes from a single institution that may not reflect the precise data concerning PC in our country, and novel therapeutic options were not available in our health care system to improve patient outcomes in mCRPC. Despite these limitations, this study optimized the use of available data to offer a comprehensive view of patients' characteristics, treatment modalities available at our institution, and treatment impact.

## Conclusion:

Our study on metastatic prostatic patients in Assiut university hospital as a model of patients in developing countries, has presented information about patient characteristics, some prognostic factors, treatment modalities and pattern of failure, showing that ADT was a successful first-line treatment with OS and PFS comparable to those in advanced nations. Combined hormonal treatment seems to be more effective than single therapy, while the diagnosis of CRPC worsens disease’s outcome.

**List of abbreviations:**

| | |
|---|---|
| PC | Prostate cancer |
| PS | Performance status |
| GS | Gleason score |
| ADT | Androgen deprivation therapy |
| PFS | Progression free survival |
| OS | Overall survival |
| CRPC | Castrate resistant prostate cancer |
| PSA | Prostate specific antigen |
| Gy | Gray |
| mCRPC | Metastatic Castrate resistant prostate cancer |
| CT | Computed tomography |
| MRI | Magnetic resonance imaging |
| PET CT | Positron Emission Tomography - Computed Tomography |
| ECOG | Eastern Cooperative Oncology Group |
| AR-Targeted | Androgen receptor targeted |

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