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Research Article

Metastatic Prostate Cancer: Clinical Aspects and Therapeutic Management in the Region of Thies Senegal

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ABSTRACT

Aim: To study the epidemiological, clinical and therapeutic aspects of advanced prostate cancer in Thies.

Patients and methods: This is a descriptive study over a period of 6 years (January 2012 to December 2017) involving 156 patients.

Results: The average age of our patients was 75.3 years (52 to 100 years). The annual incidence was estimated to 26.5 cases. The average time to referral was 30 months (3 months; 5 years). The main reason for consultation was urinary symptoms. Bone pain was the main extra-urinary symptoms noted in 73.71% of cases. Digital rectal examination was suggestive of cancer in the majority of cases (n=116). Mean PSA was 532.25 ng/mL (Range: 10.000-100 ng/mL). Pathological examination revealed prostatic adenocarcinoma in all patients. Gleason score ranged between 6 and 9 with an average of 7. At imaging bone metastases was found in 73.71% of cases. Other sites of metastasis were mainly pulmonary (14.10%) and hepatic. Of the cohort 156 patients were treated by hormonal therapy alone and 72 patients by hormone therapy associated with prostatic surgery.

Conclusion: The mortality remains high despite improved diagnostic and treatment.

Keywords: Cancer; Prostate; Metastasis; Surgery; Hormone therapy

INTRODUCTION

Prostate cancer is a common condition in adult men over 50 years old. It is the second most common cancer after bronchopulmonary location [1]. It is also the first cancer of the man over 50 years old and worldwide and in both sex, it represents the 5th leading cause of cancer mortality [2]. As a result, it is a real public health problem. Its incidence remains high in some less developed regions of the world, particularly in sub-Saharan Africa [3]. In 2012 in Senegal, according to the World Health Organization, prostate cancer represents the second leading cause of cancer death after liver cancer, with a crude mortality rate of 18.7% for an incidence of 19.1% [4]. Since the last decades, important progress has been made in both diagnosis and treatment of the disease, thus making it possible for the diagnosis at an early stage when treatment options with intent to cure are possible.

While therapeutic approach has changed for localized forms with radical prostatectomy and external radiotherapy, the management of metastatic fo b rms has also advanced considerably with the contribution of hormone therapy, including analogues of LH -RH.

However, in some developing countries, the diagnosis of prostate cancer is often made at advanced stages requiring palliative treatment in this case. At this metastatic stage of the disease, the evolution is uncertain and the management is delicate with a high morbidity. This situation is linked to the lack of qualified healthcare professionals, the lack of technical facilities and the lack of awareness the population. Diagnostic delays allow for localized and curable cases to evolve to metastatic stages with many challenges for the management. This study aims to study the epidemiological, clinical and therapeutic aspects of advanced or metastatic prostate cancer in the Thies region.

PATIENTS AND METHODS

This is a descriptive study over a period of 6 years (January 1, 2012 to December 31, 2017), involving 156 patients followed for metastatic prostate cancer in the various health facilities in the Thiès region (Senegal). These are the Regional Hospital of Thiès, the Saint Jean de Dieu Hospital and the EPS of Mbour. Variables of interest were

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age, geographic origin, family history of prostatic cancer, digital rectal examination findings, complete clinical examination, total PSA value, imaging results (ultrasound, standard radiography, computed tomography), metastasis status, therapeutic modalities, follow-up.

By advanced prostate cancer we mean a tumor mass that has extended beyond the capsule and invaded the lower part of the bladder; one or both seminal vesicles and which has distant lymph node and or visceral metastases. This corresponds to the TNM classification at stages: T3-T4/N0-N1/M0-M1.

Included in this study were all patients with histologically confirmed advanced prostate cancer with metastases. Patients (n=32) with localized or locally advanced prostate cancer and patients (n=46) with incomplete records (pathology not done) were excluded.

The data were collected using a questionnaire. Descriptive statistics were computed. Statistical significance was obtained with 5%.

RESULTS

During the study period, we collected 156 cases of advanced prostate cancer, with an estimated annual incidence of 26.5 cases (Table 1).

Patient mean age was 75.3 ± 9.4 years (52; 100 years). The most affected age group was 70-80 years old (39.1% of cases) (Figure 1).

Table 1: Incidence of metastatic prostate cancer during the study period.

Population followed for advanced prostate cancer		
Years	**Number of cases**	**Percentage (%)**
2012	16	10.25
2013	27	17.3
2014	23	14.74
2015	30	19.23
2016	33	21.15
2017	27	17.3
Total	**156**	**100**

The most represented profession was farmers 54.48% (n=85) followed by traders 29.48%. Sixteen percent (16%) of the patients were retired.

In our study 74% of the population was from rural areas compared to 26% who lived in urban areas.

The most frequent ethnic group was Severe followed by Wolof respectively in 30% and 26% of cases. The rest of the study population was represented by Fulani, Toucouleur and Diola.

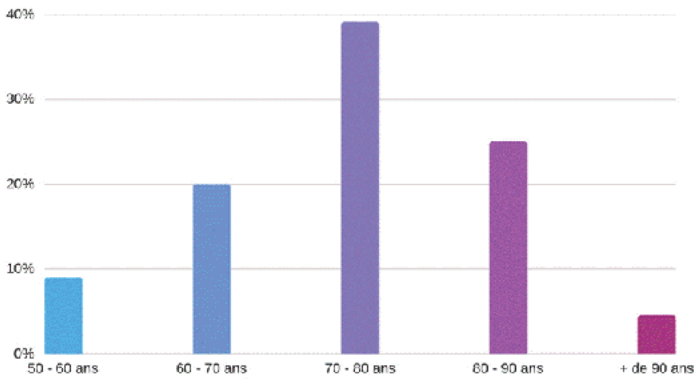

Figure 1: Distribution of patients by age group.

The voiding dysfunction were the main circumstances of diagnosis represented by weak stream 59% (n=92) and frequency 50% (n=78). The remainder of the diagnostic circumstances were represented by poor general status in 28 cases (18%) and lumbar pain in 18% of cases (Table 2).

Table 2: The different circumstances of diagnosis.

Circumstances of discovery	Numbers	Frequency (%)
Weak stream	92	59.4
Urinary frequency	78	50
Urine retention	51	33.3
General condition alteration	28	18
Lombar pain	43	27.5
Urgency	18	12.17
Hematuria	14	9
Erectile dysfonction	1	0.6
Burning micturition	10	7

High blood pressure was the most common medical history (30%), followed by type 2 diabetes with 15% of cases. Other medical history were asthma, pulmonary tuberculosis and cardiomyopathy.

In our study, 43 patients (27.5%) had a general status alteration. Nine out of 155 patients had lower limb edema. Only 3 patients had hemiplegia.

Bone pain were the main extra-urinary symptoms with 73.71% of cases followed by neurological symptoms 15%.

The rectal examination was performed in all our patients. It was suspicious of malignancy in 112 cases of cases (72%) and not suggestive of cancer in 27 patients (17%) (Figure 2).

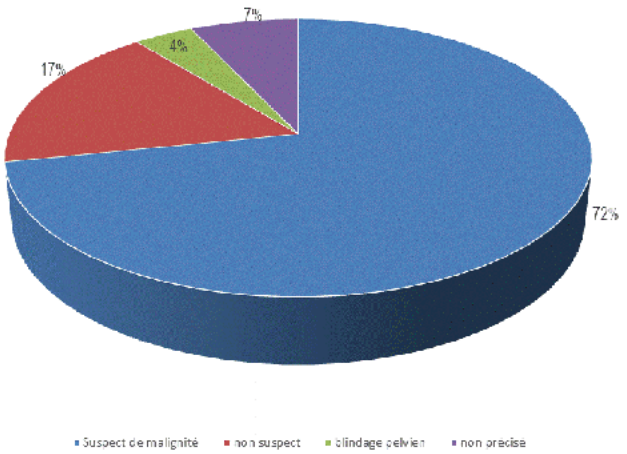

Figure 2: Results obtained at the digital rectal examination.

Blood cell count showed a mean a hemoglobin level on 11.04 g/dL (Range: 9 g/dL; 17 g/dL). Severe anemia was present in 8 cases (5%). Mean total PSA level was 532.25 ng/mL +/- 13.7 ng/mL with a median of 486 ng/mL (range: 100 ng/mL; 10,000 ng/mL) (Figure 3). Creatinine level revealed renal failure in 25 cases (16%). Urine culture was found in 60 patients showing urinary infection in 30% of cases. The most commonly found germ was *Escherichia coli*, followed by *Klebsiella Pneumoniae* with 73% and 15% respectively. The most frequent imaging modality was ultrasonography performed in all patients. In all patients the

prostate was enlarged with an average prostatic volume of 42 cc (Range: 20 cc; 130 cc). The prostate was heterogeneous in 89 patients, homogeneous in 60 other patients and unspecified in 7 cases. Spinal radiograph was available in 108 patients (69.23%).

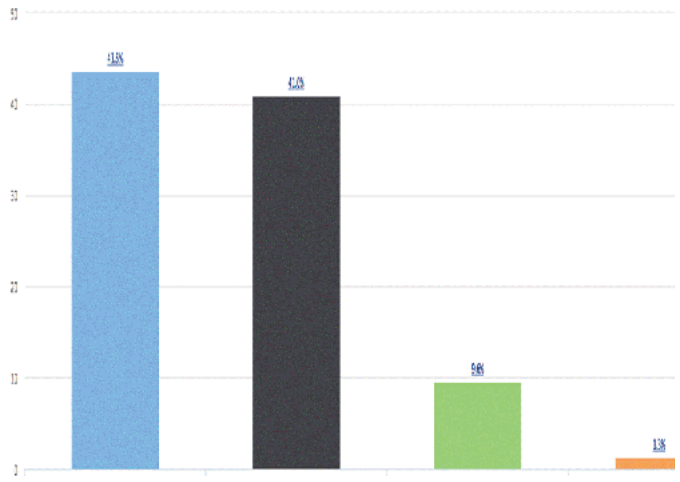

Figure 3: Distribution of total PSA level.

A total of 47 patients provided thoraco-abdomino-pelvic computed tomography (CT-TAP) and only 2 patients underwent an MRI examination: one of them had spinal cord compression with L2-L3 disc nip and geodes.

Abdominal ultrasonography was performed in 113 patients as part of the extension assessment. Ten patients (6.41% of our series) had liver metastases that were objectified on ultrasound. Upper urinary tract (HAU) abnormalities were present in 15% of patients (n=23), unilateral (n=13), bilateral (n=8) and asymmetrical (n=2) renal. Two patients had a significant post-voiding residue greater than 300 cc.

A total of 148 cases of metastases were detected with a bone predominance in 115 cases (73.71%) followed by visceral metastases essentially hepatic and pulmonary in 30 cases (19.23%) (Table 3).

Table 3: Distribution of bone metastases according to their site.

Seats of metastasis	Number	Percentage
Lumbar spine	86	55.12
Pelvic bones	29	18.58
No metastasis	41	26.28
Total	156	100

Among bone metastases, the lumbar spine was predominant, noted in 86 cases followed by pelvic localization in 18.58% of cases. Lung metastases were present in 22 cases (14%).

Pathologic examination performed in all cases showed adenocarcinoma with a mean Gleason score of 7 (range: 6-9) (Table 4).

Table 4: Distribution of Gleason score in the series.

Score of Gleason	Number	Frequency (%)
6	22	24
7	19	20
8	34	36
9	19	20
Total	156	100

All patients underwent palliative treatment. Hormonal therapy was performed in all patients. Surgical castration was performed by bilateral orchiectomy in 119 cases (76.28%) versus medical castration (22.43%). Symptomatic medical treatment was performed in 96 patients. Seventy-two patients (46.5%) underwent open prostatectomy.

Twelve patients underwent an endoscopic cervico-prostatic incision associated with hormonal therapy. In total, 154 patients (98%) benefited from medical hormone therapy. Cyproterone acetate was prescribed in 35 patients.

The follow-up of the patients under hormonal treatment varied between 1 and 8 months. The evolution was favorable in 47% of the cases with a regression of symptoms, an improvement of the general status and a notable decrease of total PSA value in 90.5% of cases. The evolution was stable in 19% of cases and unfavorable in 34% of patients. Mean initial PSA was 1991.5 ng/mL (Range: 1300; 2104 ng/mL). Average total PSA nadir was 68.55 ng/mL (with extremes of 30-130 ng/mL), a decrease of 96.5%.

The main side effects of medical hormonal treatment reported were erectile dysfunction in 25 patients, hot flushes in 20 patients. The main postoperative complications were 4 cases of immediate postoperative hemorrhage, urinary incontinence in 2 patients.A total of 46 patients (30%) were lost to follow-up. We recorded 118 cases of death, a 75.64% mortality rate due to poly-visceral failure, renal failure or respiratory distress.

Only 8% of patients (n=13) in our study experienced resistance to hormonal therapy. The mean duration of overall survival for clinically-biological and castration-resistant patients in the series was 8.6 months with a median of 6.5 months. We found an overall mean survival of 10 months. Ninety-two patients were followed up during the first year, then 68 patients in the second year (Figure 4).

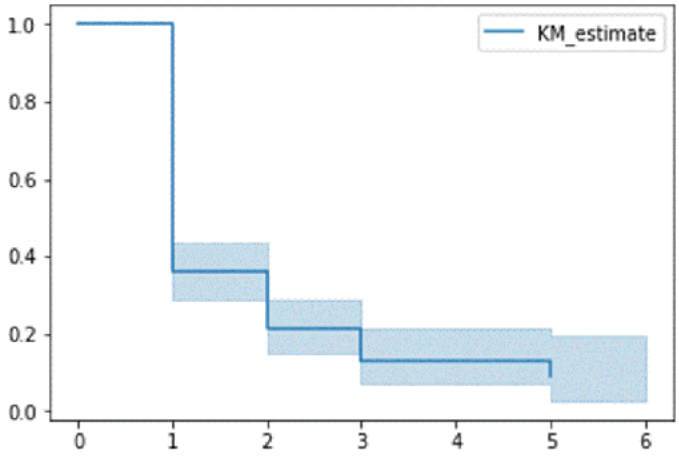

Figure 4: Survival curve of patients.

DISCUSSION

The incidence of prostate cancer is increasing worldwide [4]. In fact, in recent decades, it has become the most common cancer in adult men [5]. In our study, the incidence of advanced prostate cancer is 26.5. Osegbe [6] reported an annual incidence of 12.7. In Benin, it is the first urological cancer with an incidence of 12% [7]. In France, the incidence rate over 20 years is increased by 10,000 new cases in 1980 and 40,000 new cases in 2000, this phenomenon is explained by the aging of the population [8]. The new distribution of specialists in the regions favored increased recruitment of prostate cancer patients. However, in our context, the data are underestimated due to the absence of a cancer registry.

Age is a risk factor in the occurrence of cancer. In our series, the average age of patients is 75.3 years. Diallo et al. [9] in Guinea found the same results with an average age of 70.3 years. Like Gueye [10] in Dakar, with an average age of 71 years. According to Kaboré [11], the most represented age group was between 70 and 79 years old (70% of the study population). Sosanya [12] and Hounasso [13] found figures similar to ours with an average age of 68.3 years and 70 years respectively. There is not remarkable difference with the results found in developed countries. Indeed, Sequeira [14] in Portugal found an average age of 71.2 years. In the USA, Hofmann [15] found a median age slightly decreased by 67 years. The results confirm that the incidence of prostate cancer increases with age. The clinical stage is correlated with age at the time of diagnosis. Especially since there is often a long evolution of the disease or a persistence of mild symptoms before the patient decides to come for consultation.

Increasingly, studies are oriented to the implication of genetic factors in the genesis of prostate cancer. Thus, Niang [16] found 2 cases of family history of cancer, all related to the 1st degree. Arafa [17] has shown that 10% of the study population has a family history of prostate cancer. Tengue [18], meanwhile, reported a family history of prostate cancer (CaP) in 15% of patients. According to Alajerami [19], 22.6% of patients have a family history of CaP. In France, a study found 20% of familial forms [20]. In the US, Bentzon [21] reported that 20% of patients had a family history of CaP. In our study, we found 2 familial cases of prostate cancer. Our figures are in line with the literature and indicate that the genetic transmission of prostate cancer is to be taken into account.

The consultation period is correlated with the evolution of the disease. It remains long in developing countries, ranging from several months to a few years explaining the discovery at the late stage. In our study, the average time to consultation is 30 months. Konan [22] and Kabore [11] found a respective delay of 25.87 months and 11.6 months between the onset of symptoms and consultation. This long delay could be explained by several factors: the lack of information, the problem related to taboos, the empirical beliefs of the population preferring to be consulted initially by a traditional practitioner and the insidious evolution of the disease.

Most cancers are asymptomatic because of the latent and progressive course of the disease [23]. The existence of symptoms already reflects a locally advanced or metastatic stage. Voiding dysfunction are the major reasons for referral of prostate cancer. In our study, the circumstances of diagnosis were dominated by voiding dysfunction in 59% of cases. Our figures are supported by Gandaho [24] and Alajerami [19] who found respectively 60% and 75% of urinary symptoms.

In our series, the extra urinary symptoms constituted 18% of the reasons for referral and were mainly bone pain or neurological disorders. Botto [25] found 69% of pains of spinal origin. Magoha [26] in Naïrobi reported 64.5% of bone pain as reasons for referral.

At the metastatic stage, an Alteration of the General Status (AEG) often accompanies the clinical presentation. The proportions vary according to the authors. Thus, in our study, 27.5% of patients had an alteration of general status. In Togo, Tengue [18] found a much more significant proportion of 82.3% of patients, compared to 51.2% in Benin [18]. In 2013, Gandaho [24] noted that 44.11% of patients in his study had an impaired general status. These figures are similar to those of our study. On the other hand, our results are much lower than those of Botto [25] and Rigaud [27] in France who found respectively 47.5% and 30% of patients presenting alteration of general status. According to several authors, this alteration can constitute a circumstance of diagnosis and be a reason for consultation.

Digital Rectal Examination (DRE) remains a fundamental step in the clinical diagnosis of prostate cancer. In the advanced stage of the disease, DRE anomalies are frequent and obvious which would make it easy to guide the diagnosis. In our study, 75% of cases had a suspicious DRE. Konan [22] found 70% of cases whose diagnosis was suspected from the DRE. Niang [16] found a suggestive DRE in 87% of patients followed for advanced prostate cancer. Hounnasso [23] reported that DRE was suggestive throughout the study population. The DRE must be carried out systematically by not only urologists, but by any practitioner (general practitioners, internists, etc.). It allows to quickly orient the diagnosis and thus avoid diagnostic errors that involve costly and unnecessary investigations [24]. According to Richard [25], 15% of patients are carriers of CaP with a normal prostate at digi DRE. In our study, less than 10% of patients had a normal digital rectal exam. Thus, there may be cases of advanced prostate cancer with normal prostate at DRE.

The knowledge of the value of PSA allows easy orientation to prostate cancer. The increase in PSA is correlated with the progression of the disease so the more advanced the stage, the higher the PSA. The level of PSA is variable, as is its progression in metastatic prostate cancer. According to many African studies, patients followed for advanced prostate cancer have high PSA at the time of diagnosis [26,27]. Like Tengue [18] who found an average PSA of 315.3 ng/mL with a maximum value of 5212 ng/mL. Kaboré [11] reported a mean value of PSA of approximately 483.3 ng/mL and with 1754.7 ng/mL average PSA. In 2013 Dakar, in the same context found a total average PSA value of 1447 ng /mL with a maximum of 21660 ng/mL and more than 72% of them have a total PSA greater than 100 ng/mL. On the other hand Shalini et al. [19] and Eisenberger et al. [20] found lower values of 20 ng/mL and 161 ng/mL mean PSA, respectively. Data from Chen et al. [21] quantified the median total PSA at 154 ng/ml. The low income of patients in the face of the high cost of the exam in our context does not allow the extension of the PSA dosage. We will therefore be able to offer systematic individual screening in patients over the age of 50 as recommended by the French Urology Association (AFU).

The more advanced the stage, the higher the sensitivity of the biopsies. Adenocarcinoma is the only histological type found in our series. Our results are supported by African literature, Konan et al. [22] and Hounnasso et al. [23] found 100% biopsy-positive cases and 100% adenocarcinoma. Approximately 97.5% of patients in the Amegbor et al. [24] series had adenocarcinoma. These results are consistent with those of the literature where there is a predominance of adenocarcinoma in prostate cancer. Histological evidence was provided in 12 cases, a rate of 14.3% in Benin [25]. The Gleason score is in the majority of cases high between 7 and 9. The studies carried out & noted that 67.2% of the cases with a Gleason greater than 7. In Senegal, two studies realized found a score Gleason between 7 and 10 in the majority of cases [26]. The higher the Gleason score, the more severe the disease is and the earlier its spread. In the USA, 48% of CaP patients with bone metastases have an average Gleason of 7 [28].

Hormone therapy is the basis of treatment for advanced prostate

cancer. It is a palliative method to reduce the dependence of the condition maintained by androgens.

Bilateral testicular pulpectomy is an indication to consider. It was performed in 76.28% of patients in our series. Niang et al. [29] reported that the treatment of the Dakar population was dominated by the 43.90% pulpectomy. Surgical castration was also the most used treatment in the series of Kaboré et al. [30] and Tengue et al. [31] with respectively 43.4% and 80.5% of testicular pulpectomy performed. Surgical castration is the least expensive compared to medical hormone therapy. This explains the choice of most of the patients followed in our environment.

In a context of developing countries and lack of a system of reimbursement of expenses, cost is the determining factor in the choice of therapy. Thus, very few patients can afford medical hormonal therapy (22.43%). It is found that in Africa, the use of medical hormone therapy is generally limited by the cost, bilateral orchiectomy remains the most cost effective treatment, although it is irreversible. The influence of cost in the choice of hormone therapy has also been reported in French studies, concluding that although rarely used since the advent of LH-RH agonists, orchiectomy remains the most effective treatment [31].

Follow-up treatment is just as important as treatment itself. There is a large number of patients lost to follow up. This finding is explained by several factors: the distance from referral centers to patients' homes; lack of funding and awareness making the patients tends to stay home or prefer the traditional treatment that is ineffective on this condition.

We found an overall mean survival of 13 months. The 1 year survival rate after treatment is 91%. Thus, Sine et al. [32] found an overall mean survival time of 13.18 months. This duration is less than that reported by Fall et al. [33] which is 18.67 months. Our results are much lower than those of in France, who reported an overall average survival time of 37 months. Survival is related to histopathologic feature, stage of disease and therapeutic response.

CONCLUSION

Prostate cancer continues to be discovered at advanced stages due to delayed diagnosis. The inaccessibility of medical hormone therapy makes the treatment more challenging. Better information of the populations with the organization of regular awareness campaigns on one hand, setting up of multidisciplinary consultation meetings and improving the technical platform on the other hand will have a significant influence for an efficient management of prostate cancer in our context.

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