Metastatic Prostate Cancer under Androgen Deprivation Therapy: Factors Influencing Castration Resistance

Modou Ndiaye¹, Ousmane Sow¹*, Babacar Sine¹, Omar Gaye¹, Alioune Sarr¹, Abdoulaye Ndiath¹, Cyrille Ze Ondo¹, Amath Thiam¹, Ndeye Aissatou Bagayogo¹, Samba Thiapato Faye¹, Ndiaga Seck Ndour¹, Aboubacar Traore², Ngor Mack Thiam¹, El Hadji Malick Diaw¹, Yaya Sow¹, Boubacar Fall², Babacar Dia¹, Alain Khassim Ndoye¹

¹Urology-Andrology Department, Aristide Le Dantec Hospital, Dakar, Senegal
²Urology-Andrology Department, De la Paix Hospital, Ziguinchor, Senegal

How to cite this paper: Ndiaye, M., Sow, O., Sine, B., Gaye, O., Sarr, A., Ndiath, A., Ondo, C.Z., Thiam, A., Bagayogo, N.A., Faye, S.T., Ndour, N.S., Traore, A., Thiam, N.M., Diaw, E.H.M., Sow, Y., Fall, B., Dia, B. and Ndoye, A.K. (2020) Metastatic Prostate Cancer under Androgen Deprivation Therapy: Factors Influencing Castration Resistance. Open Journal of Urology, 10, 225-232. https://doi.org/10.4236/oju.2020.107026

Abstract

Objective: To evaluate the factors predicting the time to progression to castration-resistant in metastatic prostate cancer under Androgen Deprivation Therapy (ADT) in our center. Patients and Methods: This is a retrospective, descriptive, analytical study in a single center over a period of 2 years. It has interest patients followed for metastasized prostate cancer under ADT. The parameters studied were: epidemiological, clinical, paraclinical, prostate specific antigen (PSA) nadir, time to nadir (TTN) and their link with the castration resistance. Results: The frequency of castration resistant prostate cancer was 28 patients per year. The mean age was 70.4 ± 7.9 years. An ECOG score ≥ 3 was more common as was the cT2c stage. The median of the initial total PSA was 489.6 ng/ml (203.3; 1653.2). All patients had adenocarcinoma. The International Society of Urological Pathology (ISUP) 1 was more frequent. Bone metastases were more frequent. The medians of nadir, TTN and the castration resistance were 19.3 ng/ml (3.7; 102.1), 5.5 months (3; 9) and 11 months (6; 15.3), respectively. The Eastern Cooperative Oncology Group (ECOG) score, clinical stage, metastatic site, the nadir and its TTN influenced the DSR. Age, lymph node involvement, initial total PSA and Gleason score did not influence the castration resistance. Conclusion: ADT should be initiated as soon as possible before an attack of general and/or clinical stage advanced to delay resistance. A drilling should be associated with this hormone therapy as much as possible because of its gain on resistance.
Keywords
Cancer, Prostate, Androgen Deprivation Therapy, Resistance, Prognoses

1. Introduction
Prostate cancer is the most common cancer in older men, the second leading cause of cancer death after lung cancer and the fourth leading cause of cancer death in the general population [1]. In Senegal, most prostate cancers are diagnosed in locally advanced or metastatic stage [2] [3]. ADT the effects of which have been known for several years, is the cornerstone of the treatment of metastatic prostate cancer [4]. Bilateral pulpectomy remains the most common method in our context [2]. The hormone-sensitivity is limited in time and the biochemical progression usually takes place between 18 and 36 months after the start of hormone therapy [5]. Ten to 20% of prostate cancers progress to castration-resistant prostate cancer (CRPC) within 5 years of diagnosis, and more than 84% of newly diagnosed metastatic cancers would be CRPC [6]. The resistance to castration of metastatic prostate is now likely to be treated with new molecule. The CRPC poses a therapeutic problem in developing countries because of the accessibility and cost of these new molecules used at this stage. The objective of this study was to evaluate the factors predicting the time to progression to castration-resistant in metastatic prostate cancer under Androgen Deprivation Therapy (ADT) in our center.

2. Patients and Method
This is a retrospective, descriptive, analytical and single-center study, collecting the records of patients followed for metastasized prostate cancer between January 1, 2016 and December 31, 2017. ADT was: either medical, using analogues of luteinizing hormone-releasing hormone (Goserelin, triptorelin) or surgical, using bilateral testicular pulpectomy. A non-steroidal antiandrogen (bicalutamide) was used to complete the androgen blockade. The definition of CRPC in the CCAFU Oncology Recommendations 2016-2018 was used [7]. The general condition was evaluated by the ECOG (Eastern Cooperative Oncology Group) performance status score. Patients who had metastatic prostate cancer on hormone therapy with a complete history were included. Patients with metastatic prostate cancer receiving hormone therapy with an incomplete or unrecognized record and those with localized or metastatic prostate cancer without hormone therapy were not included. The parameters studied were: frequency, age, general condition, clinical T stage, initial total prostate specific antigen (PSA), International Society of Urological Pathology (ISUP) score 2014, lymph node involvement, metastatic sites, total PSA nadir and its TTN and their link with the castration resistance. IBM SPSS Statistics Viewer 20 software was used for statistical analysis. Prognostic factors were assessed by a multivariate analysis with the Chi-2 test
and the p value < 0.05 was considered to be statistically significant. The data were collected on a survey form from the files of patients followed in consultation or hospitalized in our department for metastatic prostate cancer under hormone therapy.

3. Results

Seventy-eight patients were included. Among them, 56 patients had CRPC. The frequency of CRPC was 28 per year. The mean age was 70.4 ± 7.9 years. The most common age groups were those between 60 and 70 and those between 70 and 80. A deterioration of the general condition with a higher ECOG score ≥ 3 was observed in 59% of patients. The clinical T stage of the tumor classified cT2c was more common, found in 55% of the patients followed by the stage cT4 observed in 36%. The median total PSA rate before treatment was 489.6 ng/ml (203.3 and 1653.2 ng/mL). Eighty-six percent (86%) of patients had a total PSA greater than 100 ng/ml. An adenocarcinoma was objectified in all patients and the ISUP score 1 was more common, found in 33% of patients. Fifty-one percent (61%) of patients did not have a regional lymph node assessment and regional lymph node involvement observed in 38% of thoracoabdominal-Computed Tomography (CT) patients. Bone metastases were more frequent, objectified in 43.6% of patients with bone scintigraphy. The median total PSA nadir was 19.3 ng/ml (3.7 and 102.1 ng/ml). The median TTN was 5.5 months (3 and 9 months). The median of the castration resistance was 11 months (6 and 15.3). Eighty-seven percent of the patients had surgical castration. This surgical castration was associated with a drilling in 19% of patients. The patients, who had surgical castration associated with drilling, had less resistance compared to the other patients (Table 1). This type of treatment influenced significantly (p 0.003) the castration resistance. The deterioration in general condition with an ECOG ≥ 3, total PSA nadir and its TTN, Metastatic sites and Clinical stage T influenced the castration resistance with significant p (Table 1 and Table 2). The patients classified CT4 were 3 times more likely to develop resistance than others with odds ration of 3.4 and a confidence interval 1.0 to 11.3. Patient age (p = 0.120), lymph node involvement (p = 0.14), initial total PSA rate, ISUP score did not affect the castration resistance with p which were not significant (Table 3).

4. Discussion

The frequency of castration resistant cancer is high in our center. This high frequency can be explained by the fact that our patients often come for consultation only at the late stage, therefore already metastasized [2] [3] [8]. In the literature, almost all prostate cancers progress to castration resistance to increasing serum PSA despite castrate levels of testosterone and progress to metastases [6]. Ten to 20% of prostate cancers progress to CRPC within 5 years of diagnosis, and more than 84% of newly diagnosed metastatic cancers are thought to be CRPC [5] [9]. The epidemiological profile of CRPC is difficult to determine due to the lack of
Table 1. Distribution of the type of treatment, the Gleason score and clinical stage based the castration resistance.

| Slice at castration resistance | Total | p  |
|--------------------------------|-------|----|
|                                |       |    |
| Not resistant                  |       |    |
| Medical castration             | 4     | 1  |
| Surgical castration            | 9     | 3  |
| Surgical castration + drilling | 9     | 2  |
| Total                          | 22    | 6  |

| Type of treatment              | 54    | 0.003 |
| Medical castration             | 9     |      |
| Surgical castration            | 3     |
| Surgical castration + drilling | 1     |
| Total                          | 78    |

| Score                          | 1     |    |
| ECOG                           |       |    |
| 0                              | 1     |    |
| 1.0                            | 13    |
| 2.0                            | 18    |
| 3.0                            | 29    |
| 4.0                            | 17    |
| Total                          | 78    |

| Clinical T stage               | 28    | 0.019 |
| cT2b                           | 4     |      |
| cT2c                           | 16    |
| cT3c                           | 3     |
| cT4                            | 28    |
| Total                          | 78    |

Table 2. Distribution of metastatic sites according to castration resistance.

| Slice at castration resistance | Total | p  |
|--------------------------------|-------|----|
|                                |       |    |
| Not resistant                  |       |    |
| M1a                            | 1     |    |
| M1b                            | 34    |
| M1c                            | 23    |
| MX                             | 20    |
| Total                          | 78    |

Table 3. Distribution of the total PSA slice before treatment, the total PSA nadir tranche and the TTN according to castration resistance.

| Slice at castration resistance | Total | p  |
|--------------------------------|-------|----|
|                                |       |    |
| Not resistant                  |       |    |
| Slice total                    | 22    | 6  |
| PSA < 100                      | 1     | 0  |
| PSA ≥ 100                      | 21    |
| Total                          | 78    |

| Slice total                    | 0.500 |
| PSA nadir                      |       |
| PSA < 100                      | 8     |
| PSA ≥ 100                      | 70    |
| Total                          | 78    |

| Slice total                    | 0.030 |
| PSA nadir                      |       |
| <5                              | 22    |
| 5 - 10                          | 56    |
| Total                          | 78    |

| Slice TTN                      | 0.000 |
|                                |       |
| <2                              | 6     |
| [2 - 5]                         | 33    |
| >5                              | 39    |
| Total                          | 78    |
standardized diagnostic models, reporting methods for CRPC and inconsistent terminology [10]. The average age of our series was similar to the average age of 73.3 ± 9.3 years found by Rigaud J et al. [11] when setting up their hormone therapy. Age was not a prognostic factor for the resistance that occurred in our series, which was consistent with the results of Mulders et al. [12]. However, Emrich et al. [13] found that age was a prognostic factor in their series. A deterioration in the general condition with an ECOG score of 3 more frequently objectified in our series could be explained by the fact that, this cancer is characterized in our regions by its diagnosis most often late, at a locally advanced or metastatic stage [3] [14]. This deterioration of the general condition was a prognostic factor in our series, as it was in most of the major series in the literature in single or multivariate analysis [15] [16] [17] [18]. Several African authors have also shown that this deterioration of the general condition with an ECOG score greater than or equal to 2 decreases survival [3] [14]. The clinical stage T2c was more frequent in our series which confirms that the tumor was advanced at diagnosis. The clinical stage of the tumor was an important prognostic factor, which was comparable to the results of Emrich et al. [13]. However Rigaud et al. [11] and Mulders et al. [12] had concluded that the clinical stage T of the primary tumor was not a prognostic factor. The level of total PSA before treatment did not influence the castration resistance as shown by Rigaud et al. [11]. In contrary, the results of Robinson et al. [19] showed that this pre-treatment total PSA level was a prognostic factor in patients treated with androgen suppression for prostate cancer. ISUP score has a disputed prognostic value in the case of advanced prostate cancer treated with hormone therapy. For some, the ISUP score has no influence on survival [12] [13] [18] but for others, a low ISUP score was a factor of good prognosis on survival in uni and multivariate analysis [17] [20]. The high Gleason (ISUP 4 and 5) score is a factor in the poor prognosis of prostate cancer in a study by Sine et al. [21] in Senegal and Gagnat et al. [22] in France. Indeed this hypothesis is confirmed by our series where the Gleason score (ISUP score) influenced the castration resistance. There was no significant difference between whether or not there was regional lymph node involvement, unlike Halabi et al. [23] who found in their study influence. The absence of regional lymph node assessment in our series could be explained by the fact that the patients were seen at an advanced stage with an impairment of renal function probably due to an invasion of the ureteral meatus making difficult the extension assessment by a thoraco-abdominal CT. It could also be explained by the lack of financial means of some patients in our regions.

An impact of the metastatic site on the castration resistance in our series has been proven by several authors in the literature [22] [23].

The PSA nadir was a significant influence on the castration resistance in our series that has been confirmed by several authors in the literature [9] [19] [22] [24] [25]. The median TTN in our series was short compared to those found in the literature. In effect Gagnat et al. [22] reported a median of TTN to 13.1
months. Most of the patients in our series had a prostate cancer already metastasized castration resistant which could explain this short time observed in our series. The study by Choueiri et al. [24] showed for the first time that the TTN was a significant prognostic factor for overall survival in metastatic prostate which complies our results. Currently in the literature several authors confirmed this impact on the occurrence of resistance [22] [26].

5. Conclusion

At the metastatic stage, ADT should be started as soon as possible before general involvement and/or an advanced clinical stage to delay resistance. Drilling for a cytoreduction must also be done as much as possible because of its gain on the occurrence of resistance to castration of metastatic prostate cancer under ADT.

Conflict of Interest Statement

All the authors do not have any possible conflicts of interest.

References

[1] Siegel, R.L., Miller, K.D. and Jemal, A. (2015) Cancer Statistics, 2015. CA: A Cancer Journal for Clinicians, 65, 5-29. https://doi.org/10.3322/caac.21254

[2] Fall, B., Tengue, K., Sow, Y., Sarr, A., Thiam, A., Mohamed, S., et al. (2012) Place de la pulpectomie bilatérale dans la suppression androgénique pour cancer de la prostate. Progrès en Urologie, 22, 344-349. https://doi.org/10.1016/j.purol.2011.12.005

[3] Gueye, S.M., Jalloh, M., Labou, I., Niang, L., Kane, R. and Ndoye, M. (2004) Profil clinique du cancer de la prostate au Sénégal. African Journal of Urology, 10, 203-207.

[4] Huggins, C. and Hodges, C.V. (1972) Studies on Prostatic Cancer. I. The Effect of Castration, of Estrogen and Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate. CA: A Cancer Journal for Clinicians, 22, 232-240. https://doi.org/10.3322/canjclin.22.4.232

[5] Khoury, S. (2012) Cancer de la prostate Hormono-indépendant. Progrès en Urologie, 1202, 7-18.

[6] Crawford, E.D., Petrylak, D. and Sartor, O. (2017) Navigating the Evolving Therapeutic Landscape in Advanced Prostate Cancer. Urologic Oncology, 35, 1-13. https://doi.org/10.1016/j.urolonc.2017.01.020

[7] Rozet, F., Hennequin, C., Beauval, J.-B., Beuzeboc, P., Cormier, L., Fromont, G., et al. (2016) Recommandations en onco-urologie 2016-2018 du CCAFU: Cancer de la prostate. Progrès en Urologie, 27, 95-144. https://doi.org/10.1016/S1166-7087(16)30705-9

[8] Niang, L., Ndoye, M., Ouattara, A., Jalloh, M., Labou, M., Thiam, I., et al. (2013) Cancer de la prostate: Quelle prise en charge au Sénégal? Progrès en Urologie, 23, 36-41. https://doi.org/10.1016/j.purol.2012.09.002

[9] Higano, C.S. and Crawford, E.D. (2011) New and Emerging Agents for the Treatment of Castration-Resistant Prostate Cancer. Urologic Oncology, 29, 1-8. https://doi.org/10.1016/j.urolonc.2011.08.013

[10] Wade, C. and Kyprianou, N. (2018) Profiling Prostate Cancer Therapeutic Resistance. International Journal of Molecular Sciences, 19, 904.
[11] Rigaud, J., Le Normand, L., Karam, G., Glémain, P., Buzelin, J.-M. and Bouchot, O. (2002) Facteurs pronostiques du cancer de la prostate traité par hormonothérapie de première intention. *Progrès en Urologie*, 12, 232.

[12] Mulders, P.F., Dijkman, G.A., Fernandez del Moral, P., Theeuwes, A.G. and Debruyne, F.M. (1990) Analysis of Prognostic Factors in Disseminated Prostatic Cancer. An Update. Dutch Southeastern Urological Cooperative Group. *Cancer*, 65, 2758-2761. https://doi.org/10.1002/1097-0142(19900615)65:12<2758::AID-CNCR2820651225>3.0.CO;2-6

[13] Emrich, L.J., Priore, R.L., Murphy, G.P. and Brady, M.F. (1985) Prognostic Factors in Patients with Advanced Stage Prostate Cancer. *Cancer Research*, 45, 5173-5179.

[14] Angwafo, F.F. (1998) 3rd. Re: Prostate Cancer in Nigerians: Facts and Nonfacts. *Journal of Urology*, 160, 135. https://doi.org/10.1016/S0022-5347(01)63068-4

[15] Chodak, G.W., Vogelzang, N.J., Caplan, R.J., Soloway, M. and Smith, J.A. (1991) Independent Prognostic Factors in Patients with Metastatic (Stage D2) Prostate Cancer. The Zoladex Study Group. *JAMA*, 265, 618-621. https://doi.org/10.1001/jama.1991.03460050072023

[16] Oosterlinck, W., Mattelaer, J., Casselman, J., Van Velthoven, R., Derde, M.P. and Kaufman, L. (1997) PSA Evolution: A Prognostic Factor during Treatment of Advanced Prostatic Carcinoma with Total Androgen Blockade. Data from a Belgian Multicentric Study of 546 Patients. *Acta Urologica Belgica*, 65, 63-71.

[17] Oosterlinck, W., Mattelaer, J., Derde, M.P. and Kaufman, L. (1995) Prognostic Factors in Advanced Prostatic Carcinoma Treated with Total Androgen Blockade. Flutamide with Orchiectomy or with LHRH Analogues. A Belgian Multicentric Study of 546 Patients. *Acta Urologica Belgica*, 63, 1-9.

[18] Jørgensen, T., Kanagasingam, Y., Kaalhus, O., Tveten, K.J., Bryne, M., Skjorten, F., et al. (1997) Prognostic Factors in Patients with Metastatic (Stage D2) Prostate Cancer: Experience from the Scandinavian Prostatic Cancer Group Study-2. *Journal of Urology*, 158, 164-170. https://doi.org/10.1016/S0022-5347(17)38081-3

[19] Robinson, D. (2008) Prediction of Survival of Metastatic Prostate Cancer Based on Early Serial Measurements of Prostate Specific Antigen and Alkaline Phosphatase. *Journal of Urology*, 179, 117-123. https://doi.org/10.1016/j.juro.2007.08.132

[20] Johansson, J.E., Andersson, S.O., Holmberg, L. and Bergström, R. (1991) Prognostic Factors in Progression-Free Survival and Corrected Survival in Patients with Advanced Prostatic Cancer: Results from a Randomized Study Comprising 150 Patients Treated with Orchiectomy or Estrogens. *Journal of Urology*, 146, 1327-1333. https://doi.org/10.1016/S0022-5347(17)38081-3

[21] Sine, B., Bagayogo, N.A., Thiam, A., Sarr, A., Zakou, A.R., Faye, S.T., et al. (2016) Cancers de la prostate de score de Gleason supérieur ou égal à 8: Evaluation de la survie des patients. *African Journal of Urology*, 22, 243-248. https://doi.org/10.1016/j.afju.2016.01.011

[22] Gagnat, A., Larré, S., Fromont, G., Pirès, C., Doré, B. and Irani, J. (2011) La survie est associée au délai d’atteinte du PSA nadir (DAN) et au ratio DAN/valeur nadir après suppression androgénique pour cancer de prostate. *Progrès en Urologie*, 21, 341-348. https://doi.org/10.1016/j.purol.2010.09.024

[23] Halabi, S., Kelly, W.K., Ma, H., Zhou, H., Solomon, N.C., Fizazi, K., et al. (2016) Meta-Analysis Evaluating the Impact of Site of Metastasis on Overall Survival in Men With Castration-Resistant Prostate Cancer. *Journal of Clinical Oncology*, 34,
[24] Choueiri, T.K., Xie, W., D’Amico, A.V., Ross, R.W., Hu, J.C., Pomerantz, M., et al. (2009) Time to Prostate-Specific Antigen Nadir Independently Predicts Overall Survival in Patients Who Have Metastatic Hormone-Sensitive Prostate Cancer Treated with Androgen-Deprivation Therapy. Cancer, 115, 981-987. https://doi.org/10.1002/cncr.24064

[25] Nayyar, R., Sharma, N. and Gupta, N.P. (2010) Prognostic Factors Affecting Progression and Survival in Metastatic Prostate Cancer. Urologia Internationalis, 84, 159-163. https://doi.org/10.1159/000277592

[26] Hori, S., Jabbar, T., Kachroo, N., Vasconcelos, J.C., Robson, C.N. and Gnanapragasam, V.J. (2011) Outcomes and Predictive Factors for Biochemical Relapse Following Primary Androgen Deprivation Therapy in Men with Bone Scan Negative Prostate Cancer. Journal of Cancer Research and Clinical Oncology, 137, 235-241. https://doi.org/10.1007/s00432-010-0877-9