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Characteristics and progression-free survival of Afro-Caribbean men with metastatic hormone-sensitive prostate cancer at the time of diagnosis

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3 **Characteristics and progression-free survival of Afro-Caribbean men with metastatic**
4 **hormone-sensitive prostate cancer (mHSPC) at the time of diagnosis.**
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Abstract

Introduction and objectives

Metastatic hormone-sensitive prostate cancer (mHSPC) accounts for 12% of prostate cancers diagnosed in Guadeloupe according to the Guadeloupean cancer registry. Most published studies have been conducted on the Caucasian population, whereas data concerning mHSPC in the Afro-Caribbean population are lacking. We aimed to describe the patient characteristics and estimate the progression-free survival of men with mHSPC in an Afro-Caribbean population according to available treatment.

Patients and methods

This was a monocentric retrospective study that consecutively included 133 men with mHSPC between January 1, 2015 and December 31, 2019 at the University Hospital of Guadeloupe. The primary endpoint was a description of the patients' characteristics with a description of complications at diagnosis. The secondary endpoint was progression-free survival. Kaplan-Meier survival and Cox proportional hazard analyses were performed.

Results

The median age at diagnosis was 71 years. The median PSA was 147 ng/ml and 37% of patients presented with a disease-related complication at diagnosis. The survival analysis according to treatment showed median survival of 15 months for the androgen deprivation (ADT) + chemotherapy group, 20 months for the ADT + new hormone therapy group, and 21.5 months for the ADT alone group, with no significant difference between the three therapeutic options (log rank test: 0.27). In univariate analysis, none of the patient characteristics at diagnosis (i.e., age, PSA, bone lesions, visceral lesions) were significantly associated with the risk of progression, regardless of the treatment.

Conclusion

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3 There was no significant difference in terms of progression-free survival between currently
4 validated treatments administered in the first line, regardless of the tumor volume or risk group.
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7 Future studies with larger numbers of patients and involving molecular factors are required to
8 confirm or invalidate these results and understand the evolution of prostate cancer in our
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Key words: prostate cancer, mHSPC, survival, androgen deprivation, docetaxel, abiraterone,
enzalutamide

Introduction

Prostate cancer is the second most prevalent cancer in terms of incidence, with more than one million new cases per year worldwide, all stages included. It is also the fifth most prevalent cause of cancer mortality, with more than 360,000 deaths per year [1]. The incidence varies by region; it is relatively high in the industrialized countries of Europe and North America (75.8 per 100,000 people in 2018), unlike Asia (6.1 per 100,000 people in 2018), where the incidence is the lowest in the world [2, 3]. There is also a disparity according to ethno-geographic origin, with a higher incidence among men of African Sub-Saharan ancestry. Thus, in Guadeloupe, where 90% of the population is of African descent, the standardized incidence is 173 per 100,000 people, which is double that of metropolitan France. Mortality due to prostate cancer is also twice as high in Guadeloupe, with a rate of 23 per 100,000 people [4].

It is now established that age, ethnicity, and a family history of prostate cancer are the main risk factors for this cancer. The reasons for the differences in incidence are largely unknown, but likely involve an interaction between social, hormonal, environmental, and genetic factors. Upon diagnosis, prostate cancer can present in various forms, including de novo metastatic prostate cancer. There is great heterogeneity in this group of patients in terms of the histoprognostic characteristics and location of metastases. Metastatic hormone-sensitive prostate cancer (mHSPC) comprises between 6 and 10% of prostate cancers at diagnosis in Caucasian populations according to the literature. The rate of mHSPC in the Afro-American population is 4.5 to 5 times greater than that in the Caucasian population [5, 6]. There is no data on the rate of mHSPC for Afro-Caribbean men.

For many years, first-generation hormone therapy was the gold standard treatment for metastatic forms of prostate cancer. Since 2015, the advent of recent therapies, such as chemotherapy with docetaxel and second-generation hormone therapies (abiraterone,

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3 enzalutamide, apalutamide) have enriched the management options for metastatic prostate
4 cancer, with an improvement in overall and progression-free survival (PFS). [7, 8, 9, 10, 11].
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8 However, the studies involving these molecules in this clinical situation have been carried out
9 mainly on Caucasians and data is scarce for the Afro-Caribbean population.
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13 The objectives of this study were to describe the characteristics of the disease and estimate the
14 progression-free survival of Guadeloupean patients with de novo metastatic prostate cancer.
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22 **Patients and Methods**

23 *Study population*

24 This was a retrospective study of men with mHSPC at the University Hospital of Guadeloupe,
25 corresponding to approximately 60% of new cases. Guadeloupe is a French-Caribbean
26 archipelago of 410,000 inhabitants, for which most of the population (~90%) is of African
27 ancestry. In total, 133 patients were included between January 1, 2015 and December 31, 2019,
28 of whom six were excluded due to missing data.
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38 The inclusion criteria were histologically proven prostate cancer, the presence of at least one
39 bone or visceral metastasis by imaging at diagnosis (bone scan, CT scan, positron emission
40 tomography (PET scan)).
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46 Patients undergoing first-line therapy were divided into three groups: androgen deprivation
47 (ADT) alone, ADT combined with new-generation hormone therapy (NGHT), such as
48 abiraterone or enzalutamide, and ADT combined with chemotherapy by docetaxel. Two
49 patients did not receive specific anti-cancer treatments but solely supportive care.
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56 Progression after the first therapeutic line was defined by: 1) castration resistance, defined,
57 according to the French onco-urology guidelines updated in 2020, by three increases in PSA
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3 resulting in two increases of 50% above the nadir, with PSA > 2 ng/mL, the appearance of one
4 or more new CT lesions, or at least two new lesions on bone scans [12, 13]; or 2) progression
5 of a lesion according to the RECIST criteria as measured by CT: $\geq 20\%$ increase in the sum of
6 the diameters of the target lesions compared to the smallest sum of the diameters observed
7 during the study (NADIR) and an increase in the sum by at least 0.5 cm.
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15 *Data collection*

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17 The data collected for each patient included their age, PSA level, and clinical stage by rectal
18 examination at diagnosis, description and location of metastases, pathological data with
19 Gleason score, treatments in the initial phase of the disease and changes depending on the
20 history of the disease (androgen deprivation therapy, abiraterone, enzalutamide or
21 chemotherapy), side effects of treatments and complications of the course of disease, dates of
22 diagnosis, and phase of resistance to castration and progression.
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32 Missing data concerned the age at diagnosis for four patients, the PSA at diagnosis for three,
33 the digital rectal examination (DRE) at diagnosis for 39, the Gleason/ISUP score at diagnosis
34 for eight, and the date and phase of resistance to castration and progression for seven. Only the
35 medical data from the database of our department were used. The study was approved by the
36 Ethics Committee of the University Hospital of Guadeloupe and the CNIL (*Commission*
37 *Nationale de l'informatique et des libertés*); authorization number 2221855.
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46 *Statistical analysis*

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48 Analyzes were carried out according to the treatment administered in the first line, as well as
49 the tumor volume and tumor risk.
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53 A high-risk tumor corresponds to the presence of at least three bone lesions, visceral metastases,
54 and ISUP group ≥ 4 [14]. A high tumor volume is defined by visceral metastases and/or ≥ 4
55 bone metastases (including at least one outside the pelvis and spine) [8].
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3 The definition of ISUP classes according to recommendations are a Gleason score of 6 (3 + 3)
4 for group 1, 7 (majority 3) for group two, 7 (4 majority) for group 3, 8 (4 + 4, 3 + 5, or 5 + 3)
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6 for group 4, and 9 or 10 for group 5.
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10 Kaplan-Meier survival analyses were performed to estimate PFS. PFS is defined as the time
11 between the start of first-line treatment and the onset of progression. The two patients who
12 received supportive care were excluded from the survival analyses.
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18 Univariate analyses were performed according to the *Cox proportional-hazards regression*
19 model to search for predictive factors of progression. None of the variables studied were
20 significant in the univariate model and therefore multivariate analysis was not performed. All
21 tests were two-tailed and p values < 0.05 were considered statistically significant. All analyses
22 were performed using StatView software version 5.0 and MedCalc software version 17.5.
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32 **Results**

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35 In total, 127 patients with de novo hormone-naive prostate cancer were included in our study.
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37 The median age at diagnosis was 71.1 years, with a median follow-up of 22.5 months. The
38 median time to start second-line therapy was 16.4 months after diagnosis and administration of
39 first-line therapy. The median PSA at diagnosis of the disease was 147.0 ng/ml. The patients'
40 characteristics are presented in Table 1.
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48 The distribution of treatment among the patients in the cohort were as follows: 69 patients
49 (54.3%) received ADT alone, 34 (26.8%) ADT + new-generation hormone therapy (including
50 abiraterone for 32 patients and enzalutamide for two), and 22 (17.3%) ADT + docetaxel. Two
51 patients received no specific treatment due to significant deterioration in their general condition
52 and received solely supportive care.
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3 At diagnosis, 37% of patients in the study had disease-related complications. Among them,
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5 40% required an upper or lower urinary tract diversion. The occurrence of spinal cord
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7 compression occurred in 17.1% of patients who developed a complication.
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11 The distribution of patients in the three treatment groups was comparable in terms of age and
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13 complications (Table 2). On the contrary, the percentage of patients with a high-risk tumor or
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15 a high tumor volume was significantly higher for the ADT + new-generation hormone therapy
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17 and docetaxel groups.
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21 Survival analysis according to therapy showed median survival of 15 months for the ADT +
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23 chemotherapy group, 20 months for the ADT + new hormone therapy group, and 21.5 months
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25 for the ADT alone group. There was no significant difference between the three therapeutic
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27 options (Log rank test: 0.27) (Figure 1).
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31 In univariate analysis, none of the variables studied were significantly associated with the risk
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33 of progression (Table 3).
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38 **Discussion**

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41 The arrival of new therapies since 2004 has made it possible to improve the therapeutic
42
43 management of patients with mHSPC. They consist of the arrival of chemotherapy and
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45 hormonotherapy, such as docetaxel in 2004, cabazitaxel in 2010 [15], abiraterone in 2011 [16],
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47 enzalutamide in 2012 [17], and more recently, apalutamide and olaparib [10] [18], into the
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49 therapeutic arsenal, not to mention adjunct treatment with denosumab and radium 223 [19, 20].
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53 The effectiveness of these new treatments has been shown by numerous studies, conducted
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55 primarily on North American, European, and Asian populations. However, data on populations
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57 of African ancestry are scarce.
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3 The validated treatments used for mHSPC between 2015 and 2019 (inclusion period of our
4 study) were ADT alone, ADT plus docetaxel [21], ADT plus abiraterone [8, 9], and ADT plus
5 enzalutamide [7, 11]. Apalutamide is another treatment validated for this indication, but we had
6 no patients because our study predated the marketing of this molecule [10].
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12 Our study concerned Afro-Caribbean men with mHSPC. With a cohort of 127 patients included
13 in the final analysis, our study is one of the largest in terms of the number of patients of African
14 descent at this stage of the disease.
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20 We did not observe a significant difference in terms of PFS according to the three first-line
21 therapeutic options: androgen suppression alone, androgen suppression plus second-generation
22 hormone therapy (abiraterone or enzalutamide), and androgen suppression plus docetaxel.
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28 The literature reports a median duration of PFS varying from 14.4 months for ADT alone to
29 25.8 months for ADT + new-generation hormone therapy [8]. Depending on the risk factors,
30 PFS ranges from 12.8 to 25 months for first-line chemotherapy [22]. The differences between
31 published values and those of this study are certainly explained by the profile of the patients,
32 who presented tumors of higher volume and higher risk in the ADT + chemotherapy and ADT
33 + new-generation hormone therapy groups.
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40 We had significantly more patients with high-risk or high-volume tumors in the group that
41 received new-generation hormone therapy or docetaxel, in accordance with the
42 recommendations of the French Association of Urology at the time of the study. Current
43 recommendations authorize the administration of new-generation hormone therapy, regardless
44 of tumor volume or risk [13].
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51 Subgroup analyses based on risk and tumor volume were not performed in our study because
52 the numbers were not sufficient to allow a relevant analysis.
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3 Our results may be partially explained by the molecular and genetic characteristics of
4 populations of sub-Saharan origin, such as the overexpression of certain genes, such as BRCA1
5 and BRCA2. Several authors have suggested a greater potential for adhesion, migration, and
6 invasion of cancer cells, which would promote the appearance of metastases in African
7 Americans, in particular [23, 24].
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12 On the other hand, despite the emergence of the PSA assay in the 1990s, which considerably
13 reduced the incidence of patients who are immediately metastatic at diagnosis, a more marked
14 delay in diagnosis and early detection in African American populations has been observed
15 relative to Caucasian populations [25]. Indeed, the percentage of mHSPC at diagnosis varies
16 depending on the population, from 4% for the Caucasian population to 8% for the African
17 American population. Published studies have not shown a significant difference in terms of
18 overall survival between the different populations [26]. In Guadeloupe, the rate of patients who
19 are metastatic from the outset at diagnosis is approximately 12% according to data from the
20 cancer registry.
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24 We found the rate of included patients with complications related to the disease to be 37%.
25 Among them, bone complications were the most common. The presence of spinal cord
26 compression in 6.3% of the patients in the study appears to confirm the data in the literature.
27 Indeed, patients with metastases in the American population developed spinal cord compression
28 in 4.8% of cases, with African-American patients showing a greater tendency to develop spinal
29 cord compression than Caucasian patients: odds ratio of 1.75 (1.39 - 2.19) [27]. Paradoxically,
30 the Caucasian population showed a higher tendency to develop bone and vertebral fractures
31 after the initiation of hormone therapy, whereas the African-American population showed
32 better bone density and a lower risk of vertebral fracture [28].
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3 This study had several limitations, including its retrospective nature and the small sample,
4 which rendered certain subgroup analyses impossible. Another study with a large number of
5 participants that takes into account the molecular characteristics of the patients will soon begin
6 and likely lead to a better understanding and better management of de novo hormone-sensitive
7 metastatic prostate cancer.
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18 **Conclusion**

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21 Our study is among the largest in terms of the number of patients with mHSPC in an Afro-
22 Caribbean population. There was no significant difference in terms of PFS between the
23 validated first-line treatment options, regardless of the tumor volume or risk group. Future
24 studies with a larger number of patients that include the study of molecular factors are needed
25 to support these results and provide a better understanding of the evolution of prostate cancer
26 in our population and thus better prevention of complications related to the disease.
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37 **Word count: 2153 words**
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3 **Acknowledgement**
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5 There is no particular acknowledgement for this work.
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Conflict of interest

The authors declare that they have no conflict of interest.

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Figure legends

Figure 1. Progression-free survival for first-line treatment mHSPC

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Table 1. Baseline characteristics of all patients

Variables	TOTAL
Number of patients (%)	127 (100%)
	Median (range)
Age at diagnosis (years)	71.1 (50.6 – 91.4)
PSA at diagnosis (ng/ml)	147.0 (1.2 – 5857.0)
Follow-up (months)	22.5 (1.0 – 193.0)
Time to second-line treatment (months)	16.4 (0.8 – 181.9)
Time to PSA progression (months)	2.2 (1.0 – 15.2)
Time to radiological progression (months)	2.4 (1.0 – 10.3)
	Number (%)
Clinical stage	
T0/T2	22 (25.6)
T3/T4	64 (74.4)
ISUP Score	
1-2	18 (14.8)
3	29 (23.8)
4-5	75 (61.4)
Tumor volume	
Low	38 (29.9)
High	89 (70.1)
Tumor risk classification	
Low	49 (38.6)
High	78 (61.4)
Combined tumor volume and risk classification	
Low	37 (29.1)
High	90 (70.9)
First-line treatment for mHSPC	
ADT alone	69 (54.3)
ADT + abiraterone or enzalutamide*	34 (26.8)
ADT + docetaxel	22 (17.3)
Palliative care**	2 (1.6)
Adverse events	
Prostate obstruction	9 (19.1)
Obstructive renal failure	10 (21.3)
Bone pain	11 (23.4)
Spinal-cord compression	8 (17.1)
Others	9 (19.1)

* Only two patients received Enzalutamide

** Two patients did not receive any specific treatment and were discharged to palliative care.

Table 2. Patient characteristic according to first line treatment

Variables	ADT alone (N = 69) N (%)	ADT + Abiraterone or Enzalutamide (N = 34) N (%)	ADT + Docetaxel (N = 22) N (%)	P value
Age at diagnosis (years)*				
≤ 70	36 (52.9)	12 (35.3)	10 (45.5)	0.24
>70	32 (47.1)	22 (64.7)	10 (54.5)	
Adverse events				0.86
Prostate obstruction	6 (23.1)	1 (7.6)	2 (25.0)	
Obstructive renal failure	4 (15.4)	3 (23.1)	3 (37.5)	
Bone pain	7 (26.9)	3 (23.1)	1 (12.5)	
Spinal-cord compression	4 (15.4)	3 (23.1)	1 (12.5)	
Others	5 (19.2)	3 (23.1)	1 (12.5)	
Tumor volume				0.0009
Low	30 (43.5)	7 (20.6)	1 (4.5)	
High	39 (56.5)	27 (79.4)	21 (95.5)	
Tumor risk				< 0.001
Low	40 (58.0)	7 (20.6)	2 (9.1)	
High	29 (42.0)	27 (79.4)	20 (90.9)	

*Missing data: one for age at diagnosis

Table 3. Univariate analyses of predictive factors for progression

Variables	HR	95% CI	P value
Age at diagnosis (years)	1.01	0.99 – 1.04	0.37
PSA at diagnosis (ng/ml)	1.01	0.99 – 1.01	0.12
Gleason score			
< 8	1.0	–	–
≥ 8	1.14	0.73 – 1.78	0.55
Visceral disease			
No	1.0	–	–
Yes	1.04	0.47 – 2.28	0.93
Bone lesions			
≤ 3	1.0	–	–
> 3	1.44	0.94 – 2.22	0.09
Tumor volume			
Low	1.0	–	–
High	1.57	0.97 – 2.52	0.06
Tumor risk			
Low	1.0	–	–
High	1.41	0.91 – 2.19	0.13

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Figure 1. Progression-free survival for first-line treatment mHSPC

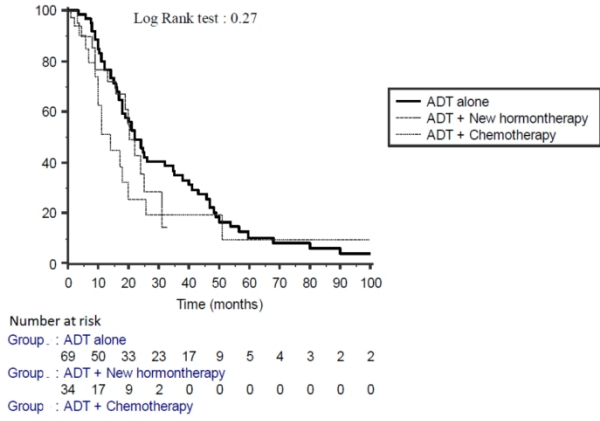


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