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Long-term survival of patients with prostate cancer in Martinique: Results of a population-based study

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ABSTRACT

Background: Martinique has one of the highest incidences of prostate cancer (PCa) worldwide. We analysed overall survival (OS) among patients with PCa in Martinique, using data from a population-based cancer registry between 2005 and 2014.

Methods: The log-rank test was used to assess the statistical differences between survival curves according to age at diagnosis, risk of disease progression including Gleason score, stage at diagnosis and Prostate Specific Antigen (PSA). A multivariable Cox model was constructed to identify independent prognostic factors for OS.

Results: A total of 5045 patients were included with a mean age at diagnosis of 68.1 ± 9.0 years [36.0 – 98.0 years]. Clinical stage was analysed in 4999 (99.1% of overall), 19.5% were at low risk, 34.7% intermediate and 36.9% at high risk. In our study, 8.9% of patients with available stage at diagnosis, were regional/metastatic cancers. Median PSA level at diagnosis was 10.4 ng/mL. High-risk PCa was more frequent in patients aged 65-74 and ≥75 years as compared to those aged < 65 years (36.6% and 48.8% versus 28.7% respectively; $p < 0.0001$). One-year OS was 96.3%, 5-year OS was 83.4 and 10-year OS was 65.0%. Median survival was not reached in the whole cohort. High-risk PCa (HR = 2.32; $p < 0.0001$), regional/metastatic stage (HR = 9.51; $p < 0.0001$) and older age (65-74 and ≥75 years - respectively HR = 1.70; and HR = 3.38), were independent prognostic factors for OS ($p < 0.0001$).

Conclusion: This study provides long term data that may be useful in making cancer management decisions for patients with PCa in Martinique.

1. Introduction

Prostate cancer (PCa) is the leading cause of cancer incidence and among the leading causes of cancer mortality in Central and South American countries [1], with a Segi-Doll world-standardized incidence rate of 79.8 and a world-standardized mortality rate of 29.0 cases per 100,000 men [2]. Martinique is an island that is an overseas department of France, and situated in the West Indies in the Caribbean. The island covers an area of 1128 km^2 with a population of 383,910 as of 2014 [3]. In terms of healthcare delivery, Martinique has a high prevalence of chronic diseases (cancer, type 2 diabetes, arterial hypertension, stroke and end-stage kidney failure). More than 1550 new cases of invasive cancer are recorded every year, with a male/female sex ratio of 1.5. With world-standardized incidence rates of 301.6 per 100,000 person-years in men, and 168.4 in women, Martinique counts among the regions of France with the lowest overall incidence of all cancers, along with Guadeloupe and French Guyana. However, the distribution of these cancers differs from that of mainland France, with large disparities for certain cancer localisations, such as the prostate, cervical cancer, stomach and multiple myeloma. Genetic factors (for prostate cancer and multiple myeloma), as well as infectious agents (HPV virus for cervical cancer, Helicobacter pylori for stomach cancer), or environmental factors (exposure to pollutants) may be implicated in the pathogenesis or exacerbation of these cancers.

Martinique has one of the highest incidence of PCa worldwide, with world-standardised incidence rate of 161.1 per 100,000 and mortality rate of 23.6 per 100,000. In Guadeloupe, the world-standardized incidence and mortality were 184.1 and 23.9 per 100,000 [4]. Puerto

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Rico has also high PCa incidence (140.7 per 100,000) and mortality (24.0 per 100,000) [5].

Most countries have limited resources to face the burden of PCa. Knowledge of survival factors is important to help cancer management. The Martinique Cancer Registry (MCR) is a high data quality, population-based cancer registry classified among the Cancer Registries of the French overseas territories, and officially certified by the Registry Evaluation Committee (Comité d'Evaluation des Registres). This committee awarded our Registry the top grade (grade A – Excellent) for the quality of its data, the expertise in public health, and for the quality of its research at national and international levels. This Registry has been participating in international epidemiological surveillance and evaluation of cancer since 1981, through the analysis of incidence and mortality data over time.

Completeness of cancer registry data is useful to inform cancer policy, monitoring of vital status and public health measures for screening programmes. Socio-demogaphic and clinical data (stage at diagnosis, Prostate specific antigen level at diagnosis, Gleason score) are recorded in the MCR database to perform epidemiological studies and evaluate the impact of cancer control programs.

African populations and their descendants have a higher incidence of PCa than other ethnic groups [6] with disparities in cancer prognosis according to stage and age. Population-based cancer registries are essential to study prognostic factor and assess survival according to these clinical data. The aim of this study was therefore to identify prognostic factor of overall survival (OS) among patients with PCa in Martinique, using data from the MCR between 2005 and 2014.

2. Methods

2.1. Population and design

The MCR performs continuous and exhaustive recording of all new PCa cases occurring in the population resident in Martinique, regardless of where the diagnosis or the treatment takes place. We included data from all patients who were diagnosed with PCa (ICD10: C61) between 2005 and 2014.

2.2. Data collection

Data were recorded in the MCR database in strict conformity with the international standards laid down by the International Agency for Research on Cancer (IARC), the French FRANCIM network, and the European Network of Cancer Registries (ENCR). Registry procedures were approved by the French National Authority for the protection of privacy and personal data. Quality control was performed in accordance with international guidelines for cancer registries.

Thanks to data crossmatching and analysis of all available data sources, in accordance with national and international guidelines, the Martinique Cancer Registry guarantees high quality information about cancer in the region of Martinique. The registry is currently actively cooperating with a range of local organisations to ensure an exhaustive data collection circuit (discharge reports, laboratory results, pathology findings, people qualified as having chronic disease by the social security, clinical patient files…).

We recorded socio-demographic data and clinical variables: year of diagnosis, age at diagnosis, zone of residence, total blood prostate-specific antigen (PSA) level at the time of diagnosis and Gleason score. Clinical stage at diagnosis was classified into localized (T1N0M0 - T2N0M0 and T3aN0M0) versus locally advanced (T3b/T4N0M0) and regional/metastatic group (N+/M+) based on the TNM classification, 7th edition (2010). Patients with missing data items were only considered to have a missing stage if there was insufficient data elsewhere to clinically stage their disease [7]. Clinical assumptions were used to impute missing staging data as follows: 1) Men with a recorded N-stage but missing M-stage have no distant metastases (M0); 2) Men with a recorded M0-stage but missing N-stage have no nodal extension (N0); 3) Men with T1-stage and a recorded Gleason score < 6 but missing N-stage and M-stage have no distant nodal extension or metastases (N0M0).

Because Martinique is a department of France, practitioners comply with national French guidelines. Accordingly, for localized disease, we stratified the patients into three risk groups [8]. For non-localized disease, we grouped the regional and metastatic categories because of the low number of patients. In clinical practice, patients who did not undergo imaging were reported as node-negative and non-metastatic. The French guidelines recommend the use of the D'Amico risk group classification, which categorizes T2c as high risk [9] contrary to the NCCN guidelines, which place T2b and T2c in the intermediate risk group [10]:

- Low risk: (1) T1a, T1b, T1c, or T2a and N0, M0; and (2) PSA level ≤10 ng/mL; and (3) Gleason score 6 or less;
- Intermediate risk: (1) T2b and N0, M0; or (2) PSA level between 10 and 20 ng/mL; or (3) Gleason score 7;
- High risk: (1) cancer stage T2c, T3a, T3b or T4, N0, M0; or (2) PSA level greater than 20 ng/mL; or (3) Gleason score between 8 and 10;
- Regional/Metastatic cancer: any N1M0, or M1.

Data regarding deaths for patients residing in Martinique were obtained from the French epidemiological center on medical causes of death from the French National Institute of Health and Medical Research (CépiDc, Inserm: http://www.cepidc.inserm.fr/site4/), ensuring completeness of death information. Active follow-up of vital status is based on medical records and administrative databases. Vital status updates and corrections of previous years are made continuously.

2.3. Statistical analysis

Patient characteristics are described as mean ± standard deviation for quantitative variables, and as number (percentage) for qualitative variables. Comparisons were performed using the Student t and Chi square or Fisher's exact tests, as appropriate.

We analyzed socio-demographic characteristics (age at diagnosis and zone of residence at the time of diagnosis) and clinical factors such as clinical stage at diagnosis, PSA, Gleason groups and risk of disease progression groups. Age was categorized into three age groups, < 65 years, 65–74 years and ≥75 years. Zone of residence was subdivided into four groups: Center, North-Atlantic, North-Caribbean, and South. The year of diagnosis was categorized into two periods, 2005–2009 and 2010–2014. We calculated OS [95% confidence interval] as the time from the date of diagnosis to the date of death from any cause. Patients were censored at the date of last follow-up, or at the cut-off date of November 7, 2015 if the patients were alive at that date. For univariate survival analysis, we used the Kaplan-Meier product-limit method to estimate the proportion of survivors over time [11]. This method allows patients with short follow-up to contribute to the estimation of survival up to the time they are censored or die, while later survival estimates are contributed by patients with longer survival, albeit with a corresponding loss of precision of the survival estimates. Confidence intervals for the survival estimates were computed using the Greenwood formula. The log-rank test was used to assess the statistical differences of the observed survival curves by each categorical variable: age groups, period of diagnosis, zone of residence, stage at diagnosis and prostate cancer risk of progression groups [12]. A multivariable Cox model for censored data was performed to identify independent prognostic factors for OS [13]. Variables with a p-value < 0.20 in the univariate analysis were included in the multivariable analysis. A p value < 0.05 was considered statistically significant. All analyses were performed using SAS version 9.4. (SAS Institute Inc., Cary, NC, USA).

Table 1
Demographic and clinical characteristics among patients with prostate cancer (N = 5045) according to age group, from the Martinique Cancer Registry.

Characteristics	All		≤64 years		65–74 years		≥75 years		*p*
	n	%	n	%	n	%	n	%	
	5045	100	1766	35.0	2011	39.9	1268	25.1	
Period of diagnosis									< 0.0001
2005–2009	2495	49.4	785	44.4	1022	50.8	688	54.3	
2010–2014	2550	50.6	981	55.6	989	49.2	580	45.7	
Zone of residence									0.0007
Center	2011	39.9	720	40.8	836	41.6	455	35.9	
North-Atlantic	1195	23.7	402	22.8	444	22.1	349	27.5	
North-Caribbean	322	6.4	99	5.6	151	7.5	72	5.7	
South	1515	30.0	545	30.8	579	28.8	391	30.9	
Unknown	2	–	0	–	1	–	1	–	
Clinical stage at diagnosis									
Localized	4455	89.1	1633	92.9	1782	89.1	1040	83.8	< 0.0001
Locally advanced	97	2.0	21	1.2	42	2.1	34	2.7	
Regional/metastatic	447	8.9	103	5.9	177	8.8	167	13.5	
Unknown	46	–	9	–	10	–	27	–	
Prostate Specific Antigen (ng/ml)									
< 4	169	3.4	88	5.0	58	2.9	23	1.8	< 0.001
4 ≥ PSA > 10	2216	44.3	945	53.8	906	45.4	365	29.3	
10 ≥ PSA > 20	1329	26.6	411	23.4	564	28.3	354	28.5	
20 ≥ PSA > 100	920	18.4	235	13.4	348	17.4	337	27.1	
≥100 ng/ml	363	7.3	78	4.4	120	6.0	165	13.3	
Unknown	48	–	9	–	15	–	24	–	
Gleason grade group									
≤6	2065	41.9	803	46.1	833	42.1	429	35.5	< 0.0001
7	1967	39.9	720	41.4	794	40.2	453	37.5	
8	561	11.4	139	8.0	221	11.2	201	16.6	
9 or 10	333	6.8	78	4.5	129	6.5	126	10.4	
Unknown	119	–	26	–	34	–	59	–	
Risk groups									< 0.0001
Low	976	19.5	471	26.8	370	18.5	135	10.9	
Intermediate	1734	34.7	679	38.6	722	36.1	333	26.8	
High	1842	36.9	504	28.7	732	36.6	606	48.8	
Regional/metastatic	447	8.9	103	5.9	177	8.8	167	13.5	
Unknown	46	–	9	–	10	–	27	–	

2.4. Ethical aspects

According to French legislation, cancer data were previously rendered anonymous with codes. The Martinique cancer registry database was approved by the French National authority for the protection of privacy and personal data (Commission Nationale Informatique et Libertés, CNIL N° 987 001). Additional approval from ethical committees was not required since our study did not involve direct patient contact.

3. Results

3.1. Patient characteristics

In total, 5045 new cases of PCa were diagnosed in Martinique between 2005 and 2014.

Table 1 presents the baseline characteristics of the PCa patients of our study. Almost 65.0% (n = 3279) were aged 65 years and older (median 68 years, range 36–98 years).

Clinical stage was available in 4999 (99.1% of overall), 19.5% were at low risk, 34.7% intermediate and 36.9% at high risk. In our study 8.9% of patients with available stage at diagnosis were regional/metastatic cancers. Median PSA level at diagnosis was 10.4 ng/mL. High-risk PCa was more frequent in patients aged 65–74 and ≥75 years as compared to those aged < 65 years (36.6% and 48.8% versus 28.7% respectively; p < 0.0001). We found that 78.1% (3479/4455) of patients with localized disease were at intermediate or high risk according to risk of disease progression. There was a statistically significant increase of advanced tumours with increasing age. Patients in the oldest age group (75+) had more advanced stage at diagnosis as compared to younger patients (Table 1).

3.2. Overall survival

One-year overall survival (OS) for the study period 2005–2014 was 96.3% [95.7–96.8], 5-year OS was 83.4 [82.2–84.6] and 10-year OS was 65.0% [62.5–67.4]. The median survival time was not reached in the total cohort. By age groups, median survival was 7.8 years (95% CI [7.3–8.5]) in those aged ≥75 years, whereas median survival was not reached in the younger age group (Fig. 1).

Table 2 presents one-, three-, and five-year OS of PCa patients by period of diagnosis, age at diagnosis, zone of residence and risk of disease progression. Fig. 2 shows OS in PCa patients, according to the risk of disease progression. The prognostic factors for OS among PCa patients are shown in Table 3.

We found that high-risk PCa (HR = 2.32; p < 0.0001), regional/metastatic stage (HR = 9.51; p < 0.0001) and older age (65–74 and ≥75 years – respectively HR = 1.70; and HR = 3.38), were independent prognostic factors for OS (all p < 0.0001).

No difference was found in our multivariable model according to zone of residence.

4. Discussion

Our study showed a long-term survival of 65% in PCa patients, ten years after diagnosis, and a 5-year OS of 83.4%. High-risk PCa,

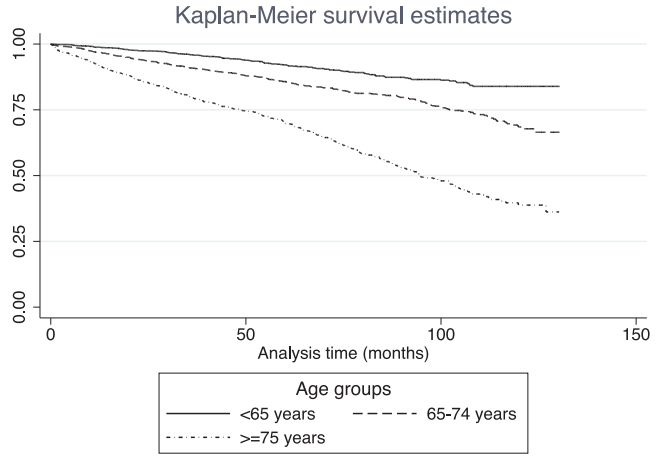

Fig. 1. Analysis of overall survival by age groups.

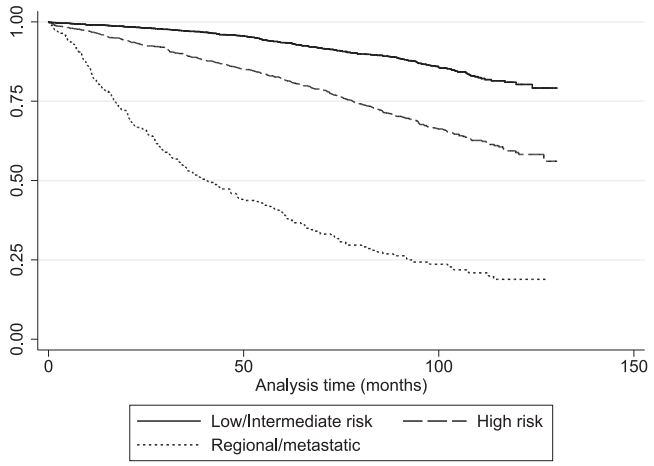

Fig. 2. Analysis of overall survival by prostate cancer risk classification group.

regional/metastatic stage and older age were independent prognostic factors for OS. We also found that 76.7% of patients with localized disease were at intermediate or high risk according to risk of disease progression. African-Caribbean men have the highest risk of PCa, with geographical variation worldwide. Research is ongoing in the Caribbean, aimed at analyzing genetic and molecular factors contributing to the difference in PCa rates in the French West-Indies compared to Metropolitan France. Several gene loci have been identified to explain the aggressive characteristics of PCa in men of African-Caribbean descent [14,15]. The role of these molecular and genetic factors need to be analysed in association with multiple other factors such as pesticide exposure, family history of PCa, and clinical management.

Differences in tumour stage and tumour burden have been investigated in African American men; racial differences in PCa outcomes in the United States have been studied to explore tumour biology and differences in cancer management in metastatic or locally advanced PCa cases [16]. Survival was significantly worse for Black men (Hazard ratio 1.27 – $p < 0.0001$). Equal access to care between white and black men was among the factors explaining racial disparities in cancer survival, and explained 84.7% of the excess risk of death in black men [16]. This study highlights the important role of cancer management factors in cancer survival. Few studies are available on stage at diagnosis in PCa patients in the Caribbean, because of the lack of high-quality population-based cancer registries in the region. One study, covering 11 French counties in 2001, showed that the proportion of localized PCa (T1 or T2) was 86.6% [17]. African-Caribbean studies on urological management of prostate cancer in Trinidad and Tobago showed that most cases were found to be high risk (63.1%) followed by intermediate risk (29.6%), and low risk (7.3%). In this latter study, intermediate and high risk groups represented 92% of all cases diagnosed [18].

Despite the higher incidence of PCa in Martinique, our study showed that prognosis was very good in these patients, a finding that has been also confirmed in international studies. Survival from PCa has been studied in Cuba, Puerto-Rico, Guadeloupe and Martinique in the CONCORD-3 study, and showed international variation in PCa survival across the Caribbean. The MCR is a member of the CONCORD working group, and the data from the patients in the present study were part of the recent CONCORD-3 study [19]. The population of Martinique (˜400,000) is extremely small, representing only 0.4% of the 100,000,000 population of Latin America [19]. In contrast, the number of PCa cases from Martinique was 6,480, representing 5.6% of the 115,102 prostate cases from all Latin America registries. Proportionally, prostate cancer is a huge burden among the population of Martinique. For men diagnosed during 2010–14, 5-year survival was approaching 100% in Puerto Rico, Martinique, and the USA; in Cuba, 5-year net survival was 71.4%. A survival study was also conducted in Guadeloupe (2008–2013 period), 5-year observed survival was 79.6% and net-survival was 90.7% [4]. Few data are available in the Caribbean regarding prostate cancer survival based on cancer registries. Due to the social disparities between Martinique and Metropolitan France, despite the same national social security system, our study could provide detailed

Table 2
Overall survival in prostate cancer patients in Martinique, 2005–2014.

Characteristics	1 year % [95% CI]	3 years % [95% CI]	5 years % [95% CI]	10 years % [95% CI]
All periods	96.3 [95.7– 96.8]	89.4 [88.5– 90.3]	83.4 [82.2– 84.6]	65.0 [62.5– 67.4]
2005–2009	95.3 [94.3–96.0]	88.4 [87.0– 89.6]	82.4 [80.8– 83.8]	64.4 [61.8– 66.8]
2010–2014	97.3 [96.5– 97.9]	90.5 [89.0– 91.8]	84.6 [82.4–86.6]	–
Zone of residence				
Center	96.0 [95.0– 96.8]	88.9 [87.3– 90.3]	83.9 [81.9– 85.7]	67.2 [63.4– 70.8]
North-Atlantic	96.6 [95.3– 97.5]	88.3 [86.1– 90.1]	81.6 [78.9– 84.0]	61.3 [55.9–66.2]
North-Caribbean	97.6 [95.0– 98.8]	93.2 [89.4– 95.7]	88.3 [83.4– 91.8]	68.0 [59.1– 75.4]
South	96.1 [94.9– 97.0]	90.2 [88.5– 91.7]	83.1 [80.8– 85.2]	64.6 [59.8– 69.1]
Age (years)				
< 65	98.8 [98.1– 99.2]	95.8 [94.6– 96.7]	92.0 [90.3– 93.4]	83.7 [80.6–86.4]
65–74	96.7 [95.8– 97.4]	90.6 [89.1– 91.9]	85.3 [83.4– 87.0]	68.0 [63.9– 71.8]
≥75	92.1 [90.4– 93.5]	79.0 [76.5– 81.3]	69.1 [66.0– 71.9]	37.9 [33.0– 42.8]
Risk groups				
Low/Intermediate	99.0 [98.5–99.3]	96.9 [96.1–97.6]	93.3 [92.1– 94.4]	80.0 [76.6– 83.0]
High	96.5 [95.5– 97.2]	88.8 [87.2– 90.3]	81.4 [79.3– 83.4]	58.2 [54.2– 62.0]
Regional/metastatic	81.6 [77.6– 85.0]	52.5[47.3– 57.5]	39.3 [33.9– 44.5]	18.1 [12.8– 24.1]

Table 3
Prognostic factors of prostate cancer survival in Martinique, 2005–2014 (N = 5045).

	Univariate HR [CI95%]	*p*	Multivariate HR [CI95%]	*p*
Period				
2005–2009	1			
2010–2014	0.85 [0.72– 1.00]	0.052		
Age				
< 65 years	1		1	
65–74 years	1.96 [1.61– 2.38]	< 0.001	1.70 [1.40– 2.07]	< 0.0001
≥75 years	4.96 [4.12– 5.98]	< 0.01	3.38 [2.79–4.09]	< 0.001
Zone of residence				
North-Caribbean	1			
Center	1.11 [0.83– 1.49]	0.473		
North-Atlantic	1.27 [0.94– 1.71]	0.116		
South	1.17 [0.87– 1.58]	0.293		
Risk groups				
Low /Intermediate	1		1	
High	2.80 [2.38– 3.30]	< 0.001	2.32 [1.97–2.74]	< 0.0001
Regional/metastatic	12.18 [10.16–14.60]	< 0.001	9.51 [7.91– 11.44]	< 0.0001

HR: hazard ratio; 95% CI: 95% confidence interval; p for Wald test of the null association.

observations regarding our region (stage at diagnosis, Gleason score, PSA level, geographic variation…) that were not covered in previous publications from CONCORD-3 or GLOBOCAN.

Although comorbidities are an important risk factor, and may reduce survival, these clinical data are unfortunately not systematically recorded in the Martinique Cancer Registry database. Population-based cancer registries only record a limited number of variables in routine activities. A study of other potentially informative covariates was performed for the incidence of the year 2013 of our database to obtain information on specific PCa treatment modalities [20]. A further analysis is planned to assess survival according to treatment modalities. Socioeconomic status, health insurance, and comorbidity were not included in this study.

Long-term survival of patients with high-risk PCa is a public health challenge, given the increase in PCa burden with increasing age. A Quality of life (QoL) study is ongoing in Martinique, with a view to extending to other countries of the Caribbean, in order to assess prognostic factors (including QoL) [21].

We expected that zone of residence could be an important survival factor. Several studies have indicated the possibility of a link between PCa and pesticides exposure [22,23]. Soil contamination by pesticides have been shown to be higher in the North-Atlantic area of Martinique [22]. Official statistics have shown wide variations of income and level of life among the counties of the island, with the lowest incomes in the North areas [24]. However, zone of residence was not significant in our analyses. On one hand, a possible explanation is the relatively short follow-up and wide confidence intervals (Table 3), which cannot confidently exclude geographical area as a survival factor. On the other hand, we note that social security covers the population for all cancer related costs, and provides for transport of patients to treatment centers. The island is mountainous but small, access to cancer treatment facilities seldom requires more than 1 h travel from any area of the island. This might explain that although area of residence has been associated with unfavourable socioeconomic levels, the effect on survival appears mitigated.

Most men with PCa are elderly patients requiring treatment based on health status and patient preference. High-risk PCa patients are often undertreated in elderly fit men; whereas there may also be overtreatment of low-risk patients, regarding comorbidities and life expectancy. Low-risk PCa patients are likely to benefit from watchful waiting or active surveillance [25]. Further analyses are needed to explore cancer survival in elderly patients. Prognostic factors for OS, especially the type of treatment (surgery, radiotherapy, androgen deprivation therapy) will be examined among the Martinique PCa cohort. This ongoing study may also help to identify disparities in factors such as access to care, sociodemographic or disease characteristics, thus focusing the attention of decision-makers and health authorities on the unmet needs for cancer care in our region [21].

5. Conclusion

This study provides long term data that may be useful in making cancer management decisions for patients with PCa in Martinique. Prognostic studies on PCa are needed in the Caribbean to assess the burden of cancer and inform optimal management. Population-based cancer registries, through their mission to perform public health surveillance and research in oncology, contribute to the development of global surveillance of cancer worldwide. This study underlines the importance of survival projects for countries of the Caribbean involved in sharing knowledge and research capacity. Further research into cancer management determinants is required to assess the role of cancer treatment, and to improve knowledge of prognostic factors in the Caribbean.

Conflict of interest

C. Joachim: no conflict of interest.
S. Ulric-Gervaise no conflict of interest.
M. Dramé: no conflict of interest.
J. Macni: no conflict of interest.
P. Escarmant: no conflict of interest.
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V. Vinh-Hung: received travel support from Ipsen.

Authorship contribution

C. Joachim, S. Ulric-Gervaise, M. Dramé, V. Vinh-Hung: Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data.

C. Joachim, S. Ulric-Gervaise, M. Dramé, J. Macni, P. Escarmant, J. Véronique-Baudin, V. Vinh-Hung: Drafting the article or revising it critically for important intellectual content.

C. Joachim, S. Ulric-Gervaise, M. Dramé, J. Macni, P. Escarmant, J. Véronique-Baudin, V. Vinh-Hung: Final approval of the version to be published.

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