

Presentation, Patterns of Care, and Outcomes of Patients With Prostate Cancer in Sub-Saharan Africa: A Population-Based Registry Study

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BACKGROUND: Although prostate cancer (PCa) is the most commonly diagnosed cancer in men of sub-Saharan Africa (SSA), little is known about its management and survival. The objective of the current study was to describe the presentation, patterns of diagnosis, treatment, and survival of patients with PCa in 10 countries of SSA. **METHODS:** In this observational registry study with data collection from 2010 to 2018, the authors drew a random sample of 738 patients with PCa who were registered in 11 population-based cancer registries. They described proportions of patients receiving recommended care and presented survival estimates. Multivariable Cox regression was used to calculate hazard ratios comparing the survival of patients with and without cancer-directed therapies (CDTs). **RESULTS:** The study included 693 patients, and tumor characteristics and treatment information were available for 365 patients, 37.3% of whom had metastatic disease. Only 11.2% had a complete diagnostic workup for risk stratification. Among the nonmetastatic patients, 17.5% received curative-intent therapy, and 27.5% received no CDT. Among the metastatic patients, 59.6% received androgen deprivation therapy. The 3- and 5-year age-standardized relative survival for 491 patients with survival time information was 58.8% (95% confidence interval [CI], 48.5%-67.7%) and 56.9% (95% CI, 39.8%-70.9%), respectively. In a multivariable analysis, survival was considerably poorer among patients without CDT versus those with therapy. **CONCLUSIONS:** This study shows that a large proportion of patients with PCa in SSA are not staged or are insufficiently staged and undertreated, and this results in unfavorable survival. These findings reemphasize the need for improving diagnostic workup and access to care in SSA in order to mitigate the heavy burden of the disease in the region. **Cancer 2021;127:4221-4232.** © 2021 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: Africa, population-based cancer registration, prostate cancer, staging, survival, treatment.

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INTRODUCTION

Prostate cancer (PCa) has become a major public health problem in sub-Saharan Africa (SSA).^{1,2} According to GLOBOCAN 2018 estimates, PCa has the highest age-standardized incidence and mortality rates of all cancers in men in SSA; rates in parts of West Africa are among the highest in the world, and the rates have been rising all over the region during the last decades.^{1,3} Studies on the uptake of screening show a lack of early-detection services and public awareness.^{4,5} Accordingly, hospital-based studies reveal that most patients present with symptomatic disease and are diagnosed at late stages.⁶ African American and Afro-Caribbean race has been associated with a more aggressive form of PCa and poorer outcomes in comparison with other population groups. This probably reflects a combination of germline susceptibility and socioeconomic and environmental factors.⁷⁻¹⁰ The stage at presentation, the Gleason score, and the prostate-specific antigen (PSA) levels are the main factors influencing PCa survival. These factors are used by international guidelines for patient risk stratification and treatment decisions, with life expectancy taken into account. Adequate treatment, consisting of either curative approaches (eg, radical prostatectomy [RP] and external-beam radiation therapy [EBRT] with or without adjuvant androgen deprivation therapy [ADT]) or active palliative approaches (eg, ADT alone), has been shown to prolong patients' survival.^{11,12}

However, the availability of these factors may be sparse in most African countries, and thus treatment decisions require local adjustment.⁴ In 2017, the National Comprehensive Cancer Network (NCCN) for the first time released harmonized PCa treatment guidelines for SSA.¹¹ This study was designed to examine contemporary, population-based presentations, diagnoses, treatments, and outcomes of patients with PCa in 10 countries of SSA and how well management complied with guideline-recommended care.

MATERIALS AND METHODS

Study Design and Data Source

In our longitudinal, population-based, observational registry study, we assembled information from 11 population-based cancer registries (PBCRs) in 10 SSA countries (Fig. 1). We collected data on the presentation, diagnostic workup, patterns of care, and factors influencing survival of patients diagnosed with PCa between 2010 and 2015. The participating PBCRs included the Registre des Cancers d'Abidjan (Côte D'Ivoire), the Addis Ababa

City Cancer Registry (Ethiopia), the Registre des Cancers du Mali (Bamako, Mali), the Registre des Cancers de Brazzaville (Congo), the Bulawayo Cancer Registry (Zimbabwe), the Cotonou Cancer Registry (Benin), the Eldoret Cancer Registry (Kenya), the Kampala Cancer Registry (Uganda), the Maputo Cancer Registry (Mozambique), the Nairobi Cancer Registry (Kenya), and the Namibian National Cancer Registry. All these registries are members of the African Cancer Registry Network (AFCRN), the African regional hub for the Global Initiative for Cancer Registry Development of the International Agency for Research on Cancer. Among the 31 AFCRN member registries from 21 countries in 2016 invited to participate in the study, the 11 aforementioned registries consented to participate in the study. The AFCRN research committee (March 2, 2016) and the respective registries' responsible bodies approved this study a priori. The PBCRs covered populations ranging from 653,000 (Bulawayo) to 4.4 million (Abidjan); they summed up to approximately 21.5 million.¹

Spending time and making efforts feasible for the given setting, we assessed the prevalence of adequate care via medical records from a random sample. A minimal sample size of 700 would produce a 2-sided 95% confidence interval (CI) with a width equal to 0.075 if the sample proportion of patients with adequate care were 0.5. We drew a simple random sample of 60 to 100 patients per registry (*International Classification of Diseases, Tenth Revision* code C61) who were registered within a 2-year period (Supporting Table 1 and Supporting Fig. 1). For Cotonou and Addis Ababa, we used all patients registered because there were fewer than 60. Patients discovered to be duplicates in the database, patients who had relapses with a date of incidence before 2010, and patients falsely registered as having PCa were excluded. Patients with additional information for diagnostics, TNM stage, therapy, or outcomes were labeled the traced cohort and were further evaluated in Kaplan-Meier survival and Cox regression analyses.

Data Collection

The PBCRs collect information on sociodemographic, clinical, and pathological characteristics, therapy, and vital status according to AFCRN's *Standard Procedure Manual*.¹³ Between September 2016 and May 2018, local staff from the PBCRs visited the health institutions to update the information of each randomly selected patient via medical charts and pathology reports. In cases without additional information traced, the patients or their relatives were called. The types of clinical data considered in

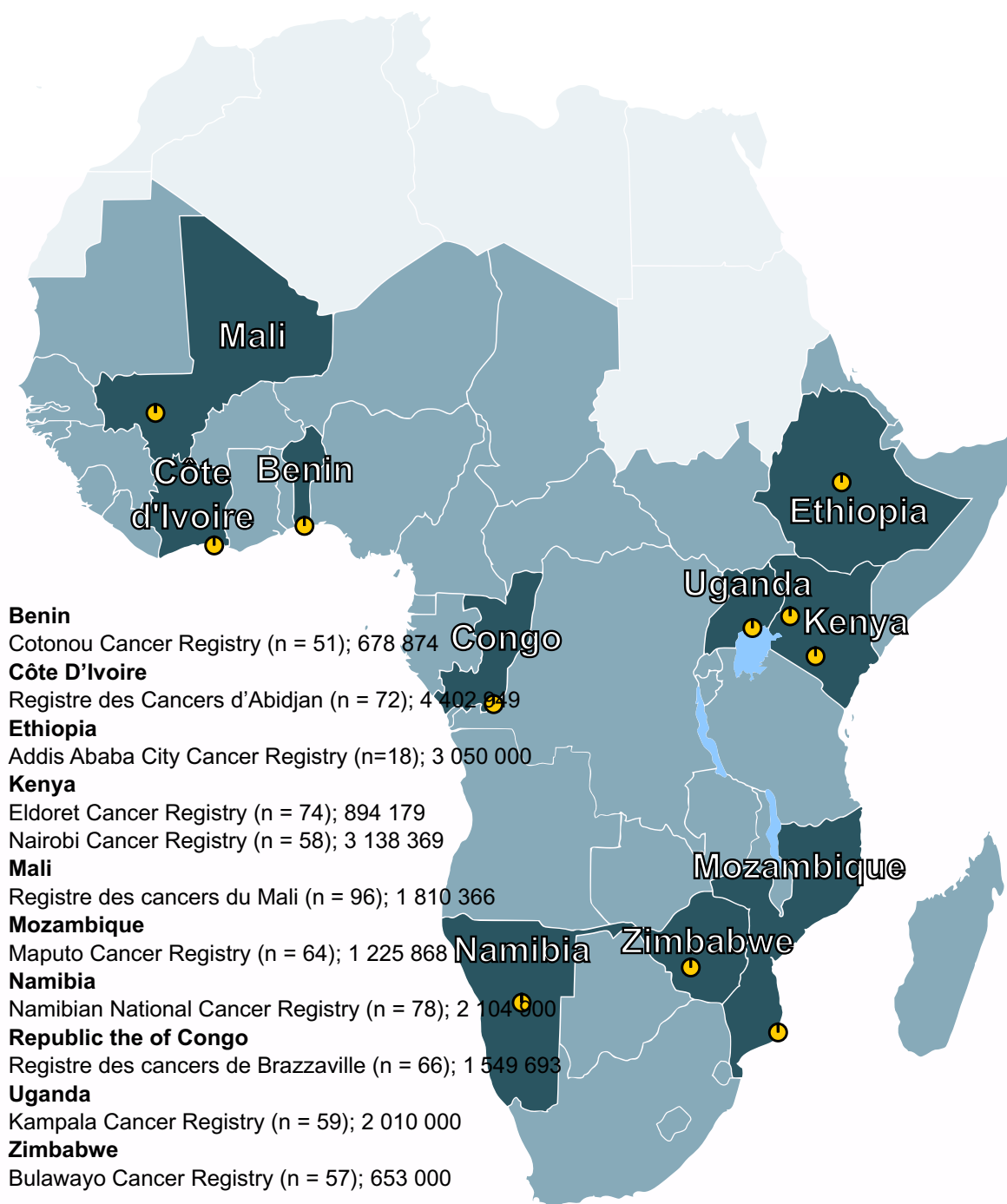


Figure 1. Countries of participating cancer registries. Countries of participating population-based cancer registries are highlighted along with the names of the registries, the number of included patients (n), and the population of each coverage area (persons).

our study included the following: PSA level at diagnosis, Gleason score, physical examination (ie, digital rectal examination [DRE]), imaging methods for staging, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and TNM stage. The types of treatment data

included surgery, radiotherapy, and endocrine therapy. We classified these with respect to cancer-directed therapy (CDT): “curative approach” (RP and EBRT with a cumulative dose of at least 60 Gy in nonmetastatic patients), “any other approach with ADT” (ADT monotherapy or

ADT with transurethral resection of the prostate, EBRT with a cumulative dose of <60 Gy, or chemotherapy), “any other approach without ADT” (transurethral resection of the prostate, EBRT with a cumulative dose of <60 Gy, or chemotherapy), and “no CDT documented” (all other cases). When the TNM stage was not documented in the record, it was derived from clinical, pathological, or imaging information with Essential TNM and the American Joint Committee on Cancer prostate cancer staging system (eighth edition).^{14,15} Accordingly, we considered the M stage to be M0 for all patients with no pathological or clinical suggestion of metastases. Patients with regional lymph node involvement documented (N1) were included in the metastatic subgroup for analysis, as were patients with an indication of lymph node involvement derived from clinical information, whereas Nx and N0 cases were included in the nonmetastatic group. We based our evaluation of the proportions of patients who received guideline-recommended diagnostic workup and care on the NCCN’s harmonized guidelines for SSA (version 2.2017).¹¹

Statistical Analysis

We used the Statistical Package for the Social Sciences (version 25) from IBM. We calculated overall survival (OS) by using the time between the date of diagnosis and the date of last known follow-up or death. We computed 1- to 5-year Ederer II age-standardized relative survival (ASRS) with Stata software (version 15) from StataCorp LLC, and we included World Health Organization life tables and adopted Corazziari et al’s International Cancer Survival Standard 1 age standard for PCa.¹⁶ We used the Kaplan-Meier method and a multivariable Cox proportional hazards model to analyze longitudinal data. We first assessed for the condition of “missing at random” (uninformative censoring) by performing a reverse Kaplan-Meier analysis. We restricted the Cox and Kaplan-Meier analyses to patients with survival longer than 3 months to allow time for the initiation of therapy and to account for bias from missing treatment through early death. In a sensitivity analysis, we studied other cutoffs. We estimated simple and multivariable hazard ratios (HRs). As covariates for adjusting the multivariable regression, we chose grouped parameters known to influence survival: TNM stage, Gleason score, PSA level at the date of diagnosis, ECOG PS, and age at diagnosis.¹¹ We followed Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for drafting this article.

RESULTS

A cohort of 693 patients (median age, 70 years; interquartile range, 64-77 years) with PCa (the total population-based cohort) was assembled from 11 PBCRs. Medical records for the extraction of additional sociodemographic and clinical data were located for 365 of the patients (52.7%; the traced cohort). For the remainder of the total population-based cohort, basic registry data could not be augmented because no additional information was retrieved by the original sources reporting the cancer diagnosis. The traced cohort (n = 365) represented 17.6% of the 2068 patients with PCa registered in the time period of random sampling in the included PBCRs (Supporting Table 1).

Patient Characteristics and Diagnostic Workup

In the traced cohort (n = 365), we identified 136 patients (37.3%) as metastatic (including 125 patients with M1 disease and 11 patients with N1 M0 disease) and 229 patients as nonmetastatic. For 55% of the traced cohort, there was no complete TNM stage documented. In the traced cohort (n = 365), 1 in 5 patients was diagnosed by clinical examination only, whereas a further 12% also had an elevated PSA level. The remaining two-thirds had pathological confirmation, with nearly all of those cases classified as adenocarcinoma. Additional patient characteristics are shown in Table 1 and Supporting Table 2. Figure 2 shows the availability of diagnostic information in our total population-based cohort (n = 693). In the nonmetastatic subgroup (n = 229), TNM stages with an unknown N status and a known N status were documented in 1 in 3 patients and in 1 in 9 patients, respectively. Thirty to forty percent of both subgroups had known PSA levels at diagnosis. We found that 26.2% of the patients had known histological confirmation of the primary but lacked documentation of the Gleason score. As for the nonmetastatic subgroup (n = 229), for 1 in 9 patients (11.2%), all 3 prognostic factors for risk stratification according to NCCN guidelines were found. Two in 5 patients in this subgroup had at least a documented T stage, which is used as a baseline parameter in the harmonized NCCN guidelines.¹¹ We found generally low rates of information from imaging. Furthermore, a small number of patients were assessed for ECOG PS.

Primary Treatment Approach

In the nonmetastatic subgroup (n = 229), 17.5% received curative-intent treatment: RP or EBRT (20 patients each). Of those patients having received EBRT, 13

TABLE 1. Patient Characteristics

Characteristic	Total Population-Based Cohort (n = 693)	Medical Records Not Available ^a (n = 328)	Traced Cohort ^b (n = 365)	Nonmetastatic Subgroup ^c (n = 229)	Metastatic Subgroup ^d (n = 136)
Age group, No. (%)					
15-54 y	35 (5.1)	16 (4.9)	19 (5.2)	10 (4.4)	9 (6.6)
55-64 y	150 (21.6)	54 (16.5)	96 (26.3)	61 (26.6)	35 (25.7)
65-74 y	234 (33.8)	98 (29.9)	136 (37.3)	79 (34.5)	57 (41.9)
75-84 y	178 (25.7)	82 (25.0)	96 (26.3)	65 (28.4)	31 (22.8)
≥85 y	43 (6.2)	25 (7.6)	18 (4.9)	14 (6.1)	4 (2.9)
Unknown age	53 (7.6)	53 (16.2)	0 (0.0)	0 (0.0)	0 (0.0)
Age, median (IQR), y	70 (64-77)	72 (64-79)	70 (63-76)	71 (62-76)	69 (63-75)
Year of diagnosis, No. (%)					
2010-2011	63 (9.1)	36 (11.0)	27 (7.4)	20 (8.7)	7 (5.1)
2012-2013	522 (75.3)	243 (74.1)	279 (76.4)	177 (77.3)	102 (75.0)
2014-2015	108 (15.6)	49 (12.5)	59 (16.2)	32 (14.0)	27 (19.9)
Highest basis of diagnosis, No. (%)					
Clinical investigation	153 (22.1)	81 (24.7)	72 (19.7)	52 (22.7)	20 (14.7)
PSA	55 (7.9)	10 (3.0)	45 (12.3)	15 (6.6)	30 (22.1)
Pathological confirmation ± PSA	432 (62.3)	184 (56.1)	248 (67.9)	162 (70.7)	86 (63.2)
Unknown basis	53 (7.6)	53 (16.2)	0 (0.0)	0 (0.0)	0 (0.0)
T stage, No. (%)					
T1 or T2			77 (21.1)	51 (22.3)	26 (19.1)
T3 or T4			72 (19.7)	38 (16.6)	34 (25.0)
Not documented			216 (59.2)	140 (61.1)	76 (55.9)
N stage, No. (%)					
N0			50 (13.7)	30 (13.1)	20 (14.7)
N1			23 (6.3)	0 (0.0)	23 (16.9)
Not documented			292 (80.0)	199 (86.9)	93 (68.4)
PSA at diagnosis, No. (%)					
<10 ng/mL			12 (3.3)	7 (3.1)	5 (3.7)
≥10 ng/mL and <20 ng/mL			7 (1.9)	5 (2.2)	2 (1.5)
≥20 ng/mL and <100 ng/mL			40 (11.0)	28 (12.2)	12 (8.8)
≥100 ng/mL			65 (17.8)	29 (12.7)	36 (26.5)
Not documented			241 (66.0)	160 (69.9)	81 (59.6)
Gleason score, No. (%)					
≤6			51 (14.0)	39 (17.0)	12 (8.8)
7			47 (12.9)	31 (13.5)	16 (11.8)
≥8			67 (18.4)	36 (15.7)	31 (22.8)
Not documented			200 (54.8)	123 (53.7)	77 (56.6)
Highest imaging for staging, No. (%)					
US only			102 (27.9)	72 (31.4)	30 (22.1)
X-ray with/without US			49 (13.4)	16 (7.0)	33 (24.3)
CT scan			31 (8.5)	8 (3.5)	23 (16.9)
MRI or bone scan			38 (10.4)	17 (7.4)	21 (15.4)
No imaging documented			145 (39.7)	116 (50.7)	29 (21.3)
ECOG PS, No. (%)					
≤1			67 (18.4)	48 (21.0)	19 (14.0)
≥2			94 (25.8)	35 (15.3)	59 (43.4)
Not documented			204 (55.9)	146 (63.8)	58 (42.6)

Abbreviations: CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; MRI, magnetic resonance imaging; PS, performance status; PSA, prostate-specific antigen; US, ultrasound.

^aPart of the total population-based cohort for which medical records were not available.

^bPart of the total population-based cohort for which medical records were available (additional clinical information).

^cSubgroup of the traced cohort comprising all patients without a pathological or clinical suggestion of metastasis (M0), including patients with an unknown lymph node status (Nx M0).

^dSubgroup of the traced cohort comprising all patients with a pathological or clinical suggestion of metastasis (M1), including all patients with a positive lymph node status (N1).

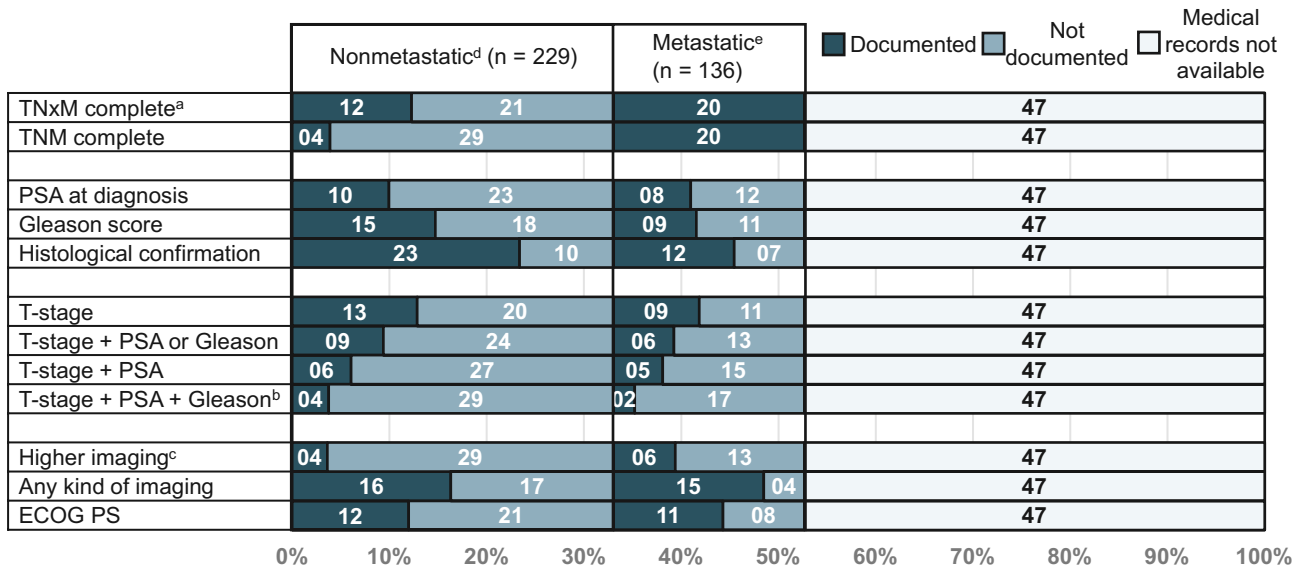


Figure 2. Availability of diagnostic information for patients with prostate cancer in the total population-based cohort (n = 693). ^aNx included. ^bMain prognostic factors according to the 2017 National Comprehensive Cancer Network guidelines. ^cFor example, computed tomography, magnetic resonance imaging, or a bone scan (used for staging). ^dThe nonmetastatic subgroup (n = 229) comprised all patients without a pathological or clinical suggestion of metastasis (M0), including patients with an unknown lymph node status (Nx M0). ^eThe metastatic subgroup (n = 136) comprised all patients with a pathological or clinical suggestion of metastasis (M1), including all patients with a positive lymph node status (N1). ECOG indicates Eastern Cooperative Oncology Group; PS, performance status; PSA, prostate-specific antigen.

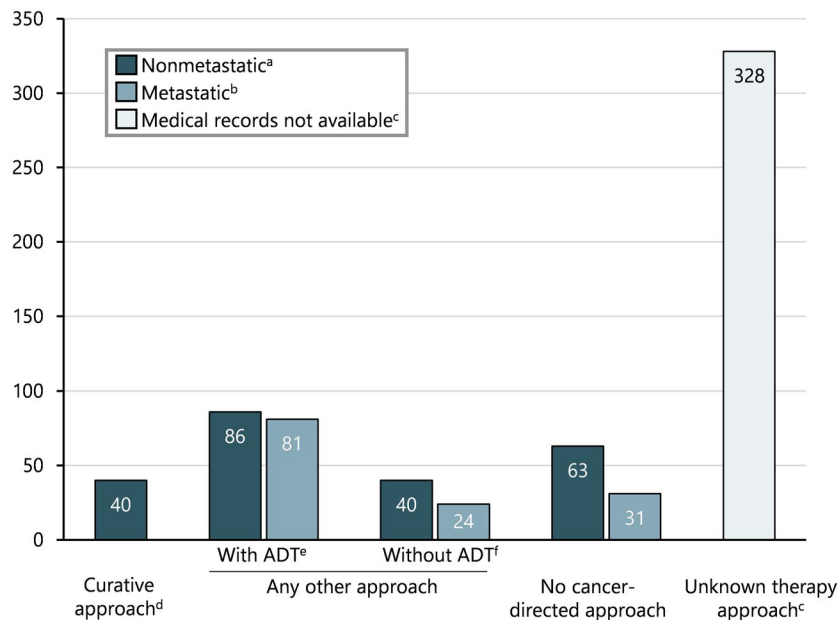


Figure 3. Primary treatment approach by identified M stage in the total population-based cohort (n = 693). ^aThe nonmetastatic subgroup (n = 229) comprised all patients without a pathological or clinical suggestion of metastasis (M0), including patients with an unknown lymph node status (Nx M0). ^bThe metastatic subgroup (n = 136) comprised all patients with a pathological or clinical suggestion of metastasis (M1), including all patients with a positive lymph node status (N1). ^cNo medical records were available for the extraction of clinical data (n = 328). ^dRadical prostatectomy or external-beam radiation therapy with a potentially curative dose. ^eADT monotherapy by surgical or medical castration or ADT by surgical or medical castration in combination with transurethral resection of the prostate or external-beam radiation therapy with a palliative dose or chemotherapy. ^fTransurethral resection of the prostate or external-beam radiation therapy with a palliative dose or chemotherapy without ADT. ADT indicates androgen deprivation therapy.

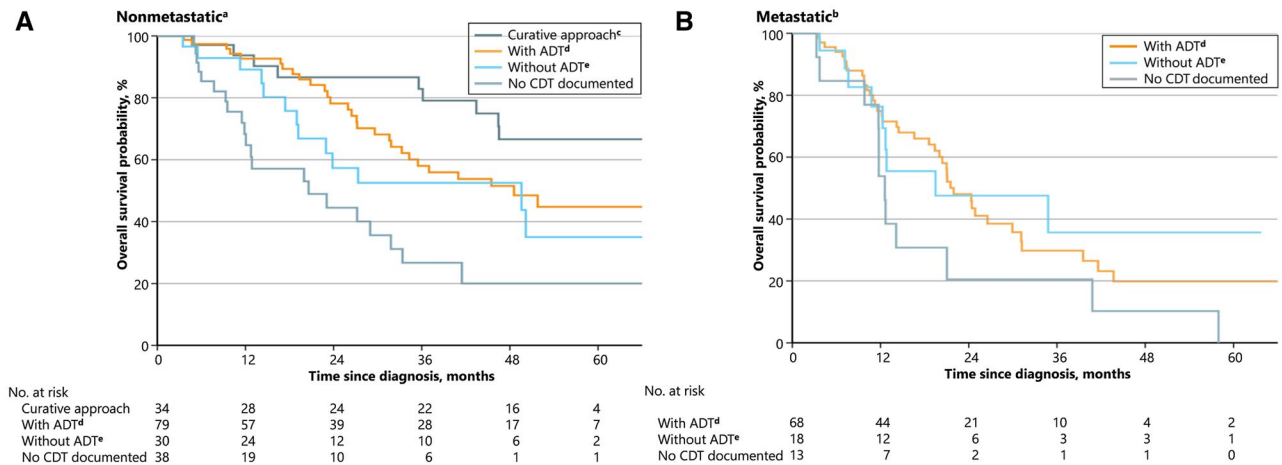


Figure 4. Overall survival of patients from the traced cohort with at least 3 months of survival stratified by M stage: differences according to the treatment approach. ^aThese patients surviving at least 3 months from the nonmetastatic subgroup (n = 181) included all patients without a pathological or clinical suggestion of metastasis (M0), including patients with an unknown lymph node status (Nx M0). ^bThese patients surviving at least 3 months from the metastatic subgroup (n = 99) included all patients with a pathological or clinical suggestion of metastasis (M1), including all patients with a positive lymph node status (N1). ^cRadical prostatectomy or external-beam radiation therapy with a potentially curative dose. ^dAny other approach with ADT by surgical or medical castration. ^eAny other approach without ADT such as transurethral resection of the prostate or external-beam radiation therapy with palliative doses. ADT indicates androgen deprivation therapy; CDT, cancer-directed therapy.

received concurrent ADT. In the nonmetastatic subgroup (n = 229), 82.5% did not receive a curative-treatment approach, with 27.5% receiving no CDT at all. The largest proportion of patients in the traced cohort (n = 365) received ADT at some point (nonmetastatic: 43.2%; metastatic: 59.6%) (Fig. 3). The ADT modalities for patients receiving any ADT were surgery (by bilateral subcapsular orchiectomy; n = 69), simple medical castration (with gonadotropin-releasing hormone agonists; n = 26), combined androgen blockade (n = 57), antiandrogen alone (mainly with bicalutamide; n = 23), and diethylstilboestrol (n = 8); 4 cases were unknown. For a quarter of the traced cohort (n = 365), no CDT was documented (Supporting Table 3).

Survival Analysis

In our total cohort (n = 693), survival data were available for 491 patients (183 deaths during observation; median follow-up, 9.3 months). The observed 1-, 3-, and 5-year OS rates were 73.3% (95% CI, 68.6%-78.0%), 42.6% (95% CI, 36.3%-48.9%), and 31.2% (95% CI, 24.5%-37.9%), respectively. The observed OS varied among the different PBCR areas (Supporting Fig. 2). The 1-, 3-, and 5-year ASRS was 82.2% (95% CI, 76.0%-86.9%), 58.8% (95% CI, 48.5%-67.7%), and 56.9% (95% CI, 39.8%-70.9%), respectively (Supporting Table 4A). When we looked at the outcomes of the traced cohort

(n = 365) stratified by M stage, the observed 1-, 3-, and 5-year OS rates for the nonmetastatic subgroup (n = 229) were 82.8% (95% CI, 77.3%-88.4%), 53.7% (95% CI, 45.5%-61.9%), and 41.1% (95% CI, 32.1%-50.2%), respectively (Supporting Table 4B). For the metastatic subgroup (n = 136), they were 61.2% (95% CI, 52.2%-70.2%), 25.8% (95% CI, 16.4%-35.2%), and 14.7% (95% CI, 5.0%-24.5%), respectively. In the Kaplan-Meier analysis of patients in the traced cohort surviving at least 3 months (n = 280), who were stratified as nonmetastatic or metastatic, we found OS differences between management approaches: in this subgroup, nonmetastatic patients (n = 181) with curative- and noncurative-treatment approaches had better OS than patients with no CDT documented (Fig. 4A). Metastatic patients (n = 99) with any form of treatment approach had better OS than patients with no CDT documented (Fig. 4B).

Multivariable Analysis

In the Cox regression analysis of patients in the traced cohort surviving at least 3 months (n = 280), who were stratified as nonmetastatic or metastatic, we found some factors influencing the probability of survival (Supporting Table 5). In the nonmetastatic subgroup, a multivariable analysis showed that “no CDT documented” (HR, 3.86; 95% CI, 1.63-9.09) and “ECOG PS \geq 2” (HR, 5.64; 95% CI, 2.46-12.94) were associated with a significantly

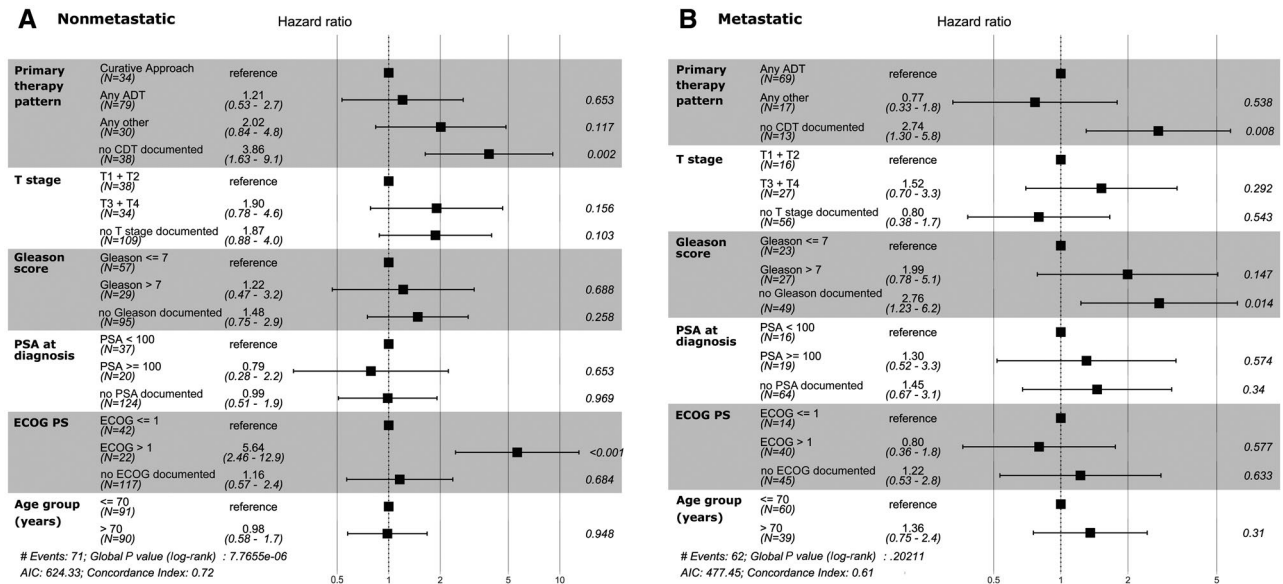


Figure 5. Forest plots showing the influence of primary treatment patterns on the survival of (A) patients with nonmetastatic prostate cancer^a and (B) patients with metastatic prostate cancer.^b The hazard ratios and 95% confidence intervals are the results of a multivariable Cox regression model adjusted for the T stage, Gleason score, PSA at diagnosis, ECOG PS, and age group. ^aThese patients surviving at least 3 months from the nonmetastatic subgroup (n = 181) included all patients without a pathological or clinical suggestion of metastasis (M0), including patients with an unknown lymph node status (Nx M0). ^bThese patients surviving at least 3 months from the metastatic subgroup (n = 99) included all patients with a pathological or clinical suggestion of metastasis (M1), including all patients with a positive lymph node status (N1). ADT indicates androgen deprivation therapy; AIC, Akaike information criterion; CDT, cancer-directed therapy; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PSA, prostate-specific antigen.

increased risk of death (Fig. 5A). In the metastatic subgroup, a multivariable analysis showed “no CDT documented” (HR, 2.74; 95% CI, 1.30-5.80) and “no Gleason score documented” (HR, 2.76; 95% CI, 1.23-6.2) were associated with a significantly increased risk of death (Fig. 5B).

A reverse Kaplan-Meier analysis (testing for uninformative censoring) suggested that in nonmetastatic and metastatic patients, most covariates had a similar pattern of censoring over time (no difference in the reverse Kaplan-Meier analysis between covariates). Especially for treatment pattern, T stage, PSA at diagnosis, and ECOG PS, censoring was at random. In the nonmetastatic subgroup, Gleason score and age at diagnosis possibly were censored not at random. In the metastatic subgroup, both of these covariates were censored at random.

DISCUSSION

This study is, to our knowledge, the first to assess the status of diagnostics, treatments, and outcomes in a random sample of population-based patients with PCa from SSA. We found that patients with PCa presented at a late stage

and lacked adequate diagnostic workup and treatment, and this led to unfavorable outcomes. A complete diagnostic workup for risk stratification, including the tumor stage, Gleason score, and PSA level, was documented for only 11% of the traced cohort (n = 365). We found that less than one-fifth of the nonmetastatic subgroup (n = 229) received therapy with curative intent. Nearly two-fifths of our traced cohort (n = 365) were diagnosed with metastatic disease. In this metastatic subgroup (n = 136), only two-thirds received ADT. In a multivariable analysis, a lack of CDT for nonmetastatic and metastatic patients was strongly associated with a higher risk of mortality.

Such a low proportion of patients with diagnostic workup and staging as required by treatment guidelines is an important limitation for adequate care. In high-income settings such as the United States, the stage is unknown for only 4% of patients with PCa, whereas it was unknown for 55% in our traced cohort.¹⁷ Several factors may contribute to the high percentage of unknown stage information in SSA. The inadequacies of local health care systems, including an undersupply of diagnostic facilities and trained staff, are a well-known problem.^{18,19} However, it is also likely that patients who might not be

able to pay for a treatment refrain from further diagnostic workup. Another challenge for PCa treatment in SSA is late presentation. Because the disease can remain asymptomatic for a long time, diagnosis at a late stage is common in settings without screening. At the time of our study, there were no general screening programs in any of the included countries; accordingly, most patients present with symptomatic disease (lower urinary tract symptoms and bone pain) and late-stage disease.⁶ It is likely that this refers to most of the included patients with an unknown stage. In high-resource settings, PSA screening is part of an ongoing, controversial discussion, although most international guidelines recommend informed decision-making for or against screening that takes into account a patient's individual risk.^{12,20} Generally, in high-income countries, routine PSA screening programs have led to a significant increase in patients with early-stage presentation.²¹ Accordingly, in a Surveillance, Epidemiology, and End Results cohort from the United States, the proportion of metastatic PCa was reported to be only 6%.¹⁷ This is in stark contrast to our traced cohort, in which more than 1 in 3 patients was known to have metastatic disease. However, a comparison of these 2 rates should be made with caution because PSA screening, starting in the 1980s in the United States, has hugely increased the total percentage of cases diagnosed at a very early stage.²²⁻²⁴ Taking into account the lack of diagnostic workup in SSA, we think that the proportion of metastatic patients is likely to have been underestimated. Hospital-based studies from Nigeria and South Africa have reported the proportion of metastatic PCa at diagnosis to be approximately 50%, although hospital series from Ghana have reported a proportion similar to ours.²⁵⁻²⁷ Early-detection programs at health facilities (DRE and targeted PSA screening in higher risk patients), together with educational programs for the population explaining the benefits of early treatment and countering the idea of a cancer diagnosis equaling death, need to be evaluated and could lead to a reduction in late-stage presentation and increase the utilization of curative-treatment approaches.

There are different treatment approaches to be considered according to the risk group, life expectancy, and patients' preferences. International guidelines propose a curative approach for all symptomatic, nonmetastatic patients.^{11,12} The low proportion of curative-treatment approaches in our population-based cohort was also seen in previous hospital-based studies in SSA. For example, only 0% and 12% of patients with PCa from Nigeria and South Africa, respectively, were managed with a curative-treatment approach.^{25,26} At the national radiotherapy

center in Ghana, 56% of patients with nonmetastatic PCa received curative radiotherapy.²⁷ In our subgroup of patients with nonmetastatic PCa, 82% did not receive curative therapy, and more than 1 in 3 patients received ADT only without RP or EBRT. Reasons for the low proportion of curative-intent treatment in our study may include a lack of specialized surgeons/urologists in the region to perform adequate RP.²⁸ Furthermore, a lack of radiotherapy machines is a major barrier to the receipt of radiotherapy in the region^{18,29} (Supporting Table 6). In contrast to our findings of relatively frequent use of ADT for nonmetastatic patients, international guidelines do not recommend the use of ADT as monotherapy for symptomatic, nonmetastatic PCa because studies have shown that the addition of adequate local therapy options improves survival significantly.^{11,12} Nevertheless, in a low-resource setting and in the absence of more adequate CDT, substandard care such as bilateral orchiectomy for symptomatic nonmetastatic disease is an economically viable treatment option and may extend patients' survival and improve their quality of life.³⁰

As expected in our cohort with many late-stage patients and substandard treatment, we found poor OS and ASRS. A lack of therapy was the second strongest predictor for an adverse outcome after a higher ECOG PS. Both nonmetastatic and metastatic patients without CDT had a 3-fold higher risk of death in comparison with patients receiving a curative treatment or ADT only. These results should be interpreted with caution because the current study is not a randomized trial of treatment, and other unmeasured prognostic factors (eg, comorbidity) may have influenced treatment allocations. Nevertheless, the outcomes of patients receiving substandard treatments such as ADT monotherapy for nonmetastatic disease were similar to those with optimal treatment. This suggests that any treatment, even with some guideline deviation, may still have a positive effect on outcomes. Our poor OS in the nonmetastatic group differs from the results observed in the radiotherapy center of Ghana, where a 5-year OS rate of 96% was found. The availability of radiotherapy and brachytherapy, as well as a selection bias of patients sent for curative therapy in Ghana, is almost certainly the reason.²⁷ CONCORD-3 found 5-year net survival rates of 58.7% and 37.8% for Nigeria (Ibadan) and South Africa (Eastern Cape), respectively.³¹ Studies from Western countries, which include a large number of early-stage PCa cases on account of PSA screening, show very high survival rates for all stages: for example, in the United States, the 5-year ASRS is 98%, and even patients with PCa with regional lymph node involvement have

a 5-year relative survival rate of approximately 100%.³² This dramatic difference in comparison with our cohort is probably a result of the broad availability of radiotherapy and surgical specialists, and a lead-time bias and overdiagnosis through general PSA testing surely play a role.³³ However, the incidence rates of PCa in the Surveillance, Epidemiology, and End Results cohort have declined steadily since 2007 and are now at the same level as they were before the PSA screening era.^{17,34} There are tremendous scarcities of investment and resources in the countries included in this study according to comparisons of their health care indicators with those of the United States (Supporting Table 6).

There are some limitations to our study. First, we could not retrieve detailed information for 47% of our total population-based cohort. Besides a notable reduction in the cohort size for subgroup analyses, we consider this also to be an important secondary finding of our study. Overall, we assume that the majority of patients without detailed information did not receive a diagnostic workup or treatment, so no medical record was initiated. Therefore, the true population-based picture may even have a higher proportion of unstaged and untreated patients. We also believe that some records were lost at random because records are handwritten, the misspelling of names is common, and record-keeping systems are often poor. We also may have missed treated patients who had left the registration area to seek treatment elsewhere. However, such patients probably represent a small proportion of all patients because our study areas were major cities, which usually provide the best cancer care in countries. Second, our survival data may reflect some bias. The treatment effect was likely overestimated in the Cox regression analysis of our study: 1) treatment was not assigned at random (healthier patients were selected), 2) patients with early deaths did not receive therapy, 3) the date of diagnosis (and, therefore, the start of the survival time) had substantial variation due to delays of the system, and 4) the degree of guideline adherence was assessed only during the survival time and not before the survival time had started (an immortal time bias). To reduce these effects, we excluded patients surviving less than 3 months (avoiding early deaths and ensuring the start of therapy for 60% of the patients). Consequently, the analysis linking therapy to survival started 3 months after diagnosis. Third, because of the shortage in diagnostic workup, we might have underestimated the proportion of metastatic patients, and some of them were included in the non-metastatic group; this resulted in poorer outcomes in this group. Consequently, we might have overestimated the

proportion of nonmetastatic patients, and this potentially led to worse outcomes. Fourth, we were unable to apply detailed risk stratification of patients because of the lack of staging information. In a setting without screening, patients present with more advanced symptomatic disease. Therefore, we assumed that all patients needed treatment rather than active surveillance because an early-stage presentation was unlikely.

Despite these limitations, our study has several important strengths. First, the patients included in the study were a random sample of all patients with PCa recorded in the study populations and not just those being referred to specialist centers. Second, the study involved 11 populations from different parts of SSA and reflected broad ranges of socioeconomic and health systems in the region. Third, we were able to evaluate the impact of different treatment approaches—from guideline-compliant optimal therapy to “no CDT at all”—on survival, which never could have been assessed in a prospective trial for ethical reasons.

In conclusion, in this population-based cohort of SSA patients with PCa, we found that for most patients, adequate clinical workup information for the assignment of treatment recommendations was lacking, and curative approaches were underused. To improve the completeness of PCa staging, more clinical training and technical equipment (eg, ultrasound, computed tomography scanning, magnetic resonance imaging, and biopsy tools) are needed. This study further validates guideline development by demonstrating that improving diagnostic workup is the first step toward the implementation of guidelines (eg, the new harmonized NCCN guidelines for SSA). To reduce the high proportion of late-stage presentation, efforts should be put into raising awareness of the disease and targeted PSA screening for higher risk patients together with opportunistic DRE screening by care providers. More radiation facilities and, in the long term, well-trained urological surgeons, radio-oncologists, and clinical oncologists are needed to provide curative-treatment approaches and thus ameliorate the outcomes of patients with PCa in SSA.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Tobias Paul Seraphin: Study concept and design, data collection, statistical analyses, interpretation of the analyses, drafting of the manuscript, and critical review and modification of the manuscript. **W. Yvonne Joko-Fru:** Statistical analyses and critical review and modification of the manuscript. **Lucia Hämmerl:** Study concept and design, data collection, and critical review and modification of the manuscript. **Mirko Griesel:** Study concept and design, data collection, and critical review and modification of the manuscript. **Nikolaus C. S. Mezger:** Data collection and critical review and modification of the manuscript. **Jana Feuchtnner:** Data collection and critical review and modification of the manuscript. **Innocent Adoubi:** Data collection and critical review and modification of the manuscript. **Marcel D. D. Egué:** Data collection and critical review and modification of the manuscript. **Nathan Okerosi:** Data collection and critical review and modification of the manuscript. **Henry Wabinga:** Data collection and critical review and modification of the manuscript. **Rolf Hansen:** Data collection and critical review and modification of the manuscript. **Samukeliso Vuma:** Data collection and critical review and modification of the manuscript. **Cesaltina F. Lorenzoni:** Data collection and critical review and modification of the manuscript. **Bourama Coulibaly:** Data collection and critical review and modification of the manuscript. **Séverin W. Odzebe:** Data collection and critical review and modification of the manuscript. **Nathan G. Buziba:** Data collection and critical review and modification of the manuscript. **Abreha Aynalem:** Data collection and critical review and modification of the manuscript. **Biying Liu:** Data collection and critical review and modification of the manuscript. **Daniel Medenwald:** Interpretation of the analyses and critical review and modification of the manuscript. **Rafael T. Mikolajczyk:** Interpretation of the analyses and critical review and modification of the manuscript. **Jason A. Efstathiou:** Interpretation of the analyses, drafting of the manuscript, and critical review and modification of the manuscript. **Donald M. Parkin:** Study concept and design, data collection, drafting of the manuscript, and critical review and modification of the manuscript. **Ahmedin Jemal:** Study concept and design, data collection, interpretation of the analyses, drafting of the manuscript, and critical review and modification of the manuscript. **Eva J. Kantelhardt:** Study concept and design, data collection, statistical analyses, interpretation of the analyses, drafting of the manuscript, and critical review and modification of the manuscript. All authors substantially contributed to the manuscript, revised and approved the final version, and agreed to submit it for publication.

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