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„Eine populationsbezogene Kohortenstudie zur onkologischen Therapie in Addis Abeba, Äthiopien“

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Referat

Die stetig steigende Anzahl maligner Erkrankungen stellt für viele Länder in Subsahara-Afrika (SSA) eine kaum zu bewältigende Herausforderung dar. Die betroffenen Gesundheitssysteme sind personell unterbesetzt und onkologische Therapieoptionen sind häufig nicht verfügbar.

In den beiden vorliegenden retrospektiven populationsbezogenen Studien werden die Therapiemodalitäten onkologischer Patient*innen in SSA näher beleuchtet. Zunächst befassen wir uns im Rahmen einer unizentrischen Studie mit der populationsbezogenen onkologischen Versorgung (Chemo- und Strahlentherapie) in der Hauptstadt von Äthiopien, Addis Abeba in den Jahren 2012 und 2014. Wir untersuchen die Wartezeit der Patient*innen bis zum Beginn der onkologischen Therapie sowie die Therapieadhärenz derjenigen Patient*innen mit den vier bzw. fünf am häufigsten diagnostizierten Tumorentitäten. Weiterhin evaluieren wir im Rahmen einer zweiten, multizentrischen Studie zum Zervixkarzinom in acht verschiedenen Ländern SSA‘s die Leitlinienadhärenz der Therapie in den Jahren 2010-2016 und ihren Zusammenhang mit dem Gesamtüberleben. Zervixkarzinom-Daten aus Addis Abeba werden hierbei mit den Daten aus sieben anderen Ländern SSA‘s verglichen.

Unserer ersten Studie zufolge hat in Addis Abeba die Hälfte der Patient*innen (54,1%) mit den fünf am häufigsten diagnostizierten Tumorentitäten, die eine chemotherapeutische Behandlung benötigten, ≥85% der geplanten Zyklen erhalten und ein Viertel der Patient*innen (24,5%) mit den vier am häufigsten diagnostizierten Tumorentitäten, die eine strahlentherapeutische Behandlung benötigten, haben ≥85% der geplanten Bestrahlungseinheiten erhalten. Die mediane Wartezeit bis zum Beginn einer Chemotherapie lag bei 2,1 Monaten und bis zum Beginn einer Strahlentherapie bei 6,9 Monaten. Unserer zweiten Studie zufolge haben in Addis Abeba nur 16,8% der Zervixkarzinompatientinnen in grundsätzlich kurativen Stadien eine onkologische Therapie mit kurativem Potential erhalten.

Die vorliegenden Studien beleuchten die onkologische Versorgung in einigen der ressourcenärmsten Länder SSA‘s. Um das Überleben nach der Diagnose einer malignen Erkrankung zu verlängern und die vielen Todesfälle in den betreffenden Ländern zu verringern bedarf es umfänglicher gesundheitspolitischer Veränderungen. Die Ergebnisse unserer beiden Studien unterstreichen insbesondere den dringenden Bedarf an zusätzlichen Bestrahlungsgeräten.

Feuchtner, Jana Cathrin: Eine populationsbezogene Kohortenstudie zur onkologischen Therapie in Addis Abeba, Äthiopien, Halle (Saale), Univ., Med. Fak., Diss., 21 Seiten, 2022

Report

Continuously rising cancer incidence rates are becoming an enormous challenge for most sub-Saharan African (SSA) countries. Health care systems are poorly staffed and oncologic treatment options are sparse.

In these two retrospective population-based cohort studies we look closer at provision of cancer care for patients in SSA. To begin with, our unicentric, population-based study in the capital of Ethiopia, Addis Ababa deals with cancer therapy (chemo- and radiotherapy) in 2012 and 2014. Firstly, we examined the time patients had to wait until the start of their cancer therapy and secondly, what level of completion patients of the four respectively five most commonly diagnosed cancer entities received within their cancer treatment. Our second study deals with cervical cancer. In this multicentric study from eight SSA countries we looked closer at guideline adherence of cancer care in 2010-2016 and its linkage to overall survival. Cervical cancer data from Addis Ababa was compared to data from seven other SSA countries.

Our first study in Addis Ababa showed that more than half (54.1%) of the five most commonly diagnosed cancer patients in need of chemotherapy received ≥85% of intended treatment cycles. A quarter (24.5%) of the four most commonly diagnosed cancer patients in need of radiotherapy received ≥85% of their radiation dose. The median waiting time for chemotherapy was 2.1 months and for radiotherapy 6.9 months. Our second study revealed that only 16.8% of cervical cancer patients in technically curable cancer stages in Addis Ababa received an oncologic treatment with a curative approach.

The present two studies shed light on the oncologic care of patients in some of the most resource-restricted countries of SSA. To improve overall survival after cancer diagnosis and to decrease the many unnecessary deaths caused by cancer in these countries, system-wide health policy measures are needed. Results of our studies especially emphasize the urgent need for additional radiation units.

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Abkürzungsverzeichnis

FIDE	Frauengesundheit in der Entwicklungszusammenarbeit
FIGO	Internationale Vereinigung für Gynäkologie und Geburtskunde
HICs	high income countries
HPV	humanes Papillomvirus
IARC	Internationale Agentur für Krebsforschung
LMICs	low and middle income countries
NHL	Non-Hodgkin-Lymphom
SSA	Subsahara-Afrika

1 Einleitung

1.1 Maligne Erkrankungen in SSA

Maligne Erkrankungen stellen global gesehen eine zunehmende gesundheitspolitische Bürde dar. In vielen Ländern sind sie eine der führenden Ursachen für einen vorzeitigen Tod sowie für schwerwiegende körperliche Beeinträchtigungen[1]. Insbesondere Länder mit niedrigem sowie mittlerem Einkommen (low and middle income countries = LMICs) sehen sich durch den epidemiologischen Wandel von infektiösen hin zu chronisch-malignen Erkrankungen mit großen Herausforderungen konfrontiert. Schätzungen zufolge wird es auf dem afrikanischen Kontinent im Jahre 2030 - im Vergleich zu 2012 - zu einem 70%igen Anstieg maligner Erkrankungen kommen[2]. Schon jetzt sind die meisten Gesundheitssysteme in SSA nicht ausreichend auf die Behandlung maligner Erkrankungen vorbereitet. Häufig fehlt es an fundamentalen Ressourcen. Errungenschaften in der Prävention, der Diagnostik und der Behandlung onkologischer Patient*innen haben bislang nur selten den Weg in den globalen Süden geschafft[3]. Die Folge dessen ist eine 1,5- bis 4-fach höhere Mortalitätsrate maligner Erkrankungen in SSA verglichen mit einkommensstarken Ländern (high income countries = HICs)[4].

1.2 Das Beispiel Äthiopien

Äthiopien ist ein ostafrikanisches Land mit einer Bevölkerung von 107 Millionen Menschen. Ein Großteil der Menschen (78,7%) lebt in ländlichen Gegenden[5]. Auch in Äthiopien sind maligne Erkrankungen zu einem rapide wachsenden gesundheitspolitischen Problem geworden. Mittlerweile sind sie die zweithäufigste Todesursache in der erwachsenen Bevölkerung[6]. Die Behandlung onkologischer Patient*innen findet in Äthiopien größtenteils im Tikur Anbessa Krankenhaus in Addis Abeba statt. Dies ist landesweit das einzige Krankenhaus mit grundlegenden onkologischen Behandlungsoptionen in der Chirurgie, Chemotherapie und Strahlentherapie. Zum Zeitpunkt der Datenerhebung (2015/2016) befand sich das einzige Bestrahlungsgerät im gesamten Land in diesem Krankenhaus[7]. Das im Jahre 2011 gegründete epidemiologische Krebsregister sammelt populationsbezogene Daten zu malignen Erkrankungen der Einwohner*innen Addis Abeba‘s, die vor dem Zeitpunkt der Diagnose ihrer malignen Erkrankung mehr als ein halbes Jahr in der Stadt gelebt haben. Über die Hauptstadtgrenzen hinaus fehlt es jedoch an einer flächendeckenden Erfassung von malignen Erkrankungen in der Bevölkerung.

1.3 Krebsregister

Populationsbezogene Krebsregister sind unabdingbar um das Ausmaß maligner Erkrankungen einschätzen und die qualitative Versorgung onkologischer Patient*innen verbessern zu können[8]. Häufig dienen sie als Informationsgrundlage für gesundheitspolitische Entscheidungen und können so maßgeblich die Versorgungsstruktur von Patient*innen positiv beeinflussen[9]. Dennoch gibt es global gesehen zwischen LMICs und HICs gravierende Unterschiede bezogen auf die Qualität und Verfügbarkeit der existierenden Krebsregister[10]. Die Internationale Agentur für Krebsforschung (IARC) und die Internationale Vereinigung von Krebsregistern haben bereits weitreichende Schritte in der Unterstützung von Krebsregistern in LMICs unternommen[11], dennoch erfüllten 2019 lediglich 24 afrikanische Krebsregister die Beitrittskriterien für eine Aufnahme in die Internationalen Vereinigung von Krebsregistern. Eines dieser Kriterien verlangt beispielsweise eine Erfassung von mindestens 70% der zu erwartenden malignen Erkrankungen im jeweiligen Registergebiet und stellt somit für viele afrikanische Krebsregister eine erste Hürde dar, da dieser Anteil häufig nicht erreicht wird[4].

1.4 Herausforderungen der onkologischen Behandlung in SSA

1.4.1 Logistische Hürden

In vielen LMICs lebt ein Großteil der Bevölkerung in ländlichen Gegenden. Dennoch befinden sich Kliniken mit umfassenden onkologischen Behandlungsoptionen meist ausschließlich in großen Städten, sie sind häufig in privater Hand und somit geographisch sowie finanziell lediglich für einen kleinen Teil der Bevölkerung zugänglich[12]. Dies führt zu einer substanziellen medizinischen Unterversorgung für Menschen aus ländlichen Gegenden. Größere Beförderungsdistanzen sind mit einem schlechteren Überleben vergesellschaftet[13]. So waren beispielsweise Frauen in Südafrika mit jeden weiteren 30 Kilometern Entfernung von der Behandlungseinrichtung um zusätzliche 25% gefährdet mit einem Mammakarzinom in einem metastasierten Stadium diagnostiziert zu werden[14]. In LMICs versterben insbesondere Menschen aus ländlichen Gegenden an den Folgen ihrer malignen Erkrankung[15].

In vielen Ländern SSA‘s existiert keine strukturierte und interdisziplinäre medizinische Erst- und Weiterversorgung onkologischer Patient*innen. Die Überweisung der Patient*innen verläuft häufig willkürlich oder findet nicht statt, sodass sich die Betroffenen eigenständig zu onkologischen Spezialist*innen navigieren müssen. Es konnte gezeigt werden, dass 43% der onkologischen Patient*innen in Kamerun zu ≥4 verschiedenen Einrichtungen überwiesen worden sind, bevor die Diagnose ihrer malignen Erkrankung gestellt werden konnte[16]. Auch wenn Patient*innen frühzeitig vorstellig werden, fehlt es oft an den technischen Mitteln um eine zeitnahe Diagnosestellung zu realisieren[17].

1.4.2 Tumorstadien

Im Gegensatz zu HICs wird der Großteil der onkologischen Patient*innen in SSA erst in fortgeschrittenen Tumorstadien diagnostiziert[18]. In Addis Abeba lag im Jahre 2015 der Anteil an Mammakarzinompatient*innen, die sich in einem fortgeschrittenen Tumorstadium befanden (Stadium 3 oder 4) bei 61%[19] und einer Studie aus dem nördlichen Äthiopien zufolge sogar bei 85%[20]. Im Vergleich hierzu lag der selbige Anteil in Kanada in den Jahren 2011-2015 bei nur 17,3%[21]. Die Tatsache, dass höhere Tumorstadien aber nicht den einzigen Grund für ein schlechteres Überleben nach einer Tumordiagnose in LMICs darstellen, konnten Weiner et al. zeigen. Demnach hatten Mammakarzinompatient*innen in einem metastasierten Stadium in Äthiopien ein deutlich schlechteres mittleres Überleben von nur 11,7 Monaten als Patient*innen im selbigen Stadium in westlichen Ländern (33 Monate). Ursächlich hierfür scheint der hohe Anteil an nicht verabreichten systemischen Therapien sowie die späte Feststellung der Metastasierung zu sein[22].

Für einen Großteil der in SSA anzutreffenden Tumorentitäten existieren effektive Präventions- und Früherkennungsmaßnahmen sowie wirksame onkologische Therapieoptionen[23]. Flächendeckende Aufklärungskampagnen zu Risikofaktoren und den Symptomen maligner Erkrankungen stellen einen ersten praktikablen Ansatz dar, um die Früherkennung bei Patient*innen zu schulen und bereits frühe Tumorstadien zeitgerecht einer adäquaten Diagnostik und Therapie zuzuführen und somit das Überleben onkologischer Patient*innen in LMICs zu verbessern[24]. So war beispielsweise in HICs vor der Einführung des Mammographie-Screenings eine Sensibilisierung für das Mammakarzinom in der Gesellschaft ein Hauptgrund für den Trend zu früheren Stadien bei der Diagnosestellung[25].

1.4.3 Kulturelle Unterschiede

Kulturelle Normen und lokale Traditionen können zusätzlich den Zugang zum Gesundheitssystem und demnach zu einer zeitnahen und kurativen onkologischen Therapie erschweren. Dies steht häufig im Zusammenhang mit einem niedrigen Bildungsniveau und einer Skepsis gegenüber der wissenschaftlich orientierten Medizin. In SSA konsultiert bis zu 80% der Bevölkerung an erster Stelle einen traditionellen Heilpraktiker bevor sie eine Einrichtung des staatlichen Gesundheitssystems aufsucht[26]. So lassen beispielsweise in der Republik Kamerun, wo die traditionelle Medizin offiziell vom Gesundheitsministerium anerkannt wird, 55% der Eltern, deren Kind an einem Burkitt-Lymphom erkrankt ist, die onkologische Therapie von einem traditionellen Heilpraktiker durchführen[27]. Die Allgegenwärtigkeit und die vergleichsweise geringen Behandlungskosten der traditionellen Medizin stellen für viele onkologische Patient*innen in SSA eine attraktive Behandlungsalternative dar und sie ist in vielen Fällen für eine erhebliche Verzögerung der Diagnosestellung verantwortlich[16].

1.4.4 Onkologische Chirurgie

Die onkologische Chirurgie ist ein wesentlicher Bestandteil in der Behandlung maligner Erkrankungen. Von den weltweit geschätzten 15,2 Millionen malignen Erkrankungen im Jahre 2015 waren in über 80% der Fälle ein bis mehrere Male eine chirurgische Behandlung notwendig. Dennoch erhalten global gesehen weniger als 25% der onkologischen Patient*innen eine sichere, zeitgerechte und finanzierbare chirurgische Behandlung. In LICs liegt dieser Anteil lediglich bei 5%[28]. Die Wahrscheinlichkeit, dass sich Patient*innen in LMICs einer chirurgischen Behandlung unterziehen, hängt wesentlich von ihren finanziellen Mitteln ab. Global gesehen erfahren 25% der Patient*innen, die sich in eine chirurgische Behandlung begeben, eine finanzielle Notlage[29].

Auch in onkologisch-palliativen Behandlungskonzepten spielen chirurgische Interventionen eine bedeutende Rolle. Studien zur Folge besteht in HICs bei 15-20% der onkologischen Palliativpatient*innen die Notwendigkeit einer chirurgischen Behandlung. In LMICs hat die palliative Chirurgie aufgrund des großen Anteils an fortgeschrittenen Tumorstadien eine besonders hohe Relevanz[28].

1.4.5 Chemotherapie

Viele Chemotherapeutika, die als unentbehrliche Arzneimittel gelistet werden, sind in SSA nicht verfügbar. Verteilungsschwierigkeiten und häufige Lieferengpässe limitieren die Nutzung der wenigen verfügbaren Chemotherapeutika[30]. In Botswana, einem LMIC mit sehr guter medizinischer Gesundheitsversorgung, waren im Jahr 2015 mindestens 40% der essentiellen Chemotherapeutika für eine mediane Zeit von einem Monat nicht verfügbar. Hierbei handelte es sich um essentielle Substanzen in der Behandlung von beispielsweise Mamma-, Zervix- und Kolonkarzinomen. Für die betroffenen Patient*innen bedeutet dies eine suboptimale Behandlung mit einer Verzögerung von Therapiezyklen, einer Reduktion von Zyklen oder der Substitution durch weniger effektive Chemotherapeutika und einem damit einhergehendem schlechteren Outcome[31]. Dennoch ist die Frage einer chemotherapeutischen Versorgung onkologischer Patient*innen nicht nur jene der Verfügbarkeit von Chemotherapeutika. Um eine sichere und effektive Chemotherapie durchführen zu können, bedarf es insbesondere auch einer ausreichend ausgebauten Infrastruktur. Dass diese Infrastruktur noch lange nicht gegeben ist, hat das Afrikanische Krebsregisternetzwerk gezeigt: Auf dem gesamten afrikanischen Kontinent gibt es lediglich 102 Institutionen, die eine onkologische Versorgung anbieten, wobei sich allein 38 dieser Einrichtungen in Südafrika befinden[27].

1.4.6 Strahlentherapie

Die Strahlentherapie ist ein wesentlicher Bestandteil sowohl in der kurativen als auch in der palliativen Behandlung onkologischer Patient*innen. Häufig sind die multimodalen onkologischen Therapiekonzepte ohne die Verfügbarkeit einer Strahlentherapie nicht realisierbar.

Dennoch erhält die Strahlentherapie eine nur sehr geringe inländische und internationale Finanzierung und in Folge dessen haben 90% der Bevölkerung in LICs keinen Zugang zu dieser Behandlungsoption[32].

Ein wichtiger Parameter zur Abschätzung der Strahlentherapiekapazität eines Landes ist das Verhältnis von Bestrahlungsgeräten zur Bevölkerungszahl. Auf dem gesamten afrikanischen Kontinent lag einer 2018 erschienenen Studie zufolge das Verhältnis bei 1: 3,56 Millionen. In Äthiopien war die Lage in den Jahren 2015 und 2016 deutlich drastischer. Hier gab es für die gesamte Bevölkerung lediglich ein Bestrahlungsgerät, entsprechend einem Verhältnis von 1:107 Millionen[33]. Im Gegensatz hierzu lag das Verhältnis in Deutschland im Jahre 2013 bei 1:130.000[34]. Dabei ist der Strahlentherapiebedarf gerade in LMICs erhöht. In HICs wird bei 52% der onkologischen Patient*innen die Strahlentherapie als Teil des Therapiekonzeptes vorgesehen, wohingegen in LMICs 60% der Patient*innen sie benötigen würden. Dies ist in LMICs am ehesten auf die weiter fortgeschrittenen Stadien bei Diagnosestellung zurückzuführen[35].

Die Ursachen für den Mangel an Bestrahlungsgeräten in LMICs sind multifaktoriell. Die Ausbildung von qualifiziertem Personal sowie der Aufbau einer geeigneten Infrastruktur stellen erste Hürden dar[36]. In Afrika bieten lediglich 18,5% der Länder Ausbildungsoptionen in onkologischer Strahlentherapie an[37]. Zudem sind die Ausgaben für die Finanzierung der Infrastruktur, die Instandhaltung sowie eine verlässliche Stromversorgung weitere Hürden in der Erhaltung und Bereitstellung von Bestrahlungsgeräten[38].

1.5 Das Zervixkarzinom in SSA und im internationalen Vergleich

Global gesehen stellt das Zervixkarzinom das vierthäufigste Malignom der Frau dar. In vielen Ländern SSA‘s steht es jedoch an erster Stelle. Die höchsten Inzidenzen finden sich in Malawi und Zimbabwe[39]. Von den weltweit geschätzten 570.000 Zervixkarzinom-Erstdiagnosen und den 311.000 Zervixkarzinom-Todesfällen aus dem Jahre 2018 ist ein hoher Prozentsatz der Fälle in SSA zu finden. So lag im Jahre 2018 der Anteil der global registrierten Zervixkarzinom-Neudiagnosen in SSA bei 20% und der Anteil der Todesfälle bei 24%, obwohl in SSA der globale Anteil der über 20-jährigen Frauen lediglich bei 9,4% liegt[40].

Der wichtigste Risikofaktor für die Entstehung eines invasiven Zervixkarzinoms ist die Infektion mit dem humanen Papillomvirus (HPV), das zahlreiche onkogenetische Subtypen aufweist[41]. Die Impfung gegen HPV stellt eines der wirksamsten Instrumente zur Prävention einer malignen Erkrankung überhaupt dar. In Kombination mit Screeningprogrammen kann eine Impfung gegen HPV das Risiko einer tödlich verlaufenden Zervixkarzinomerkrankung drastisch verringern[42]. Doch gerade in LMICs, in denen präventive Maßnahmen nicht flächendeckend zur Verfügung stehen, stellt das Zervixkarzinom weiterhin ein großes Gesundheitsrisiko dar[43]. In SSA sind

mindestens 27,8% aller malignen Erkrankungen auf eine Infektion zurückzuführen, wohingegen der Anteil in HICs bei unter 5% liegt[44]. Präventionsmaßnahmen sollten daher vor allem in LMICs einen zentralen Bestandteil in der Gesundheitspolitik darstellen.

Screeningprogramme konnten in HICs zu einer beträchtlichen Reduktion (50-80%) der Zervixkarzinominzidenz sowie zu einer Reduktion der Mortalität führen. Ursächlich hierfür ist der niederschwellige Zugang zu den Screeninguntersuchungen für die breite Bevölkerung, konsequente Folgeuntersuchungen sowie die Behandlung von zervikalen intraepithelialen Präkanzerosen[45]. In SSA wird der Großteil der aktuell existierenden Screeningmaßnahmen sporadisch durchgeführt und die Maßnahmen erfassen nur einen geringen Teil der Bevölkerung. Häufig erreichen die Programme lediglich junge Frauen die eine Krankenversicherung haben und in urbanen Gegenden wohnen. Folglich sinkt in diesen Ländern die Inzidenz und Mortalität lediglich minimal bis überhaupt nicht[46].

Durch das Fehlen von etablierten Screeningmaßnahmen wird der Großteil der Zervixkarzinome in LMICs erst in einem fortgeschrittenen Stadium gemäß der Internationalen Vereinigung für Gynäkologie und Geburtskunde (FIGO) diagnostiziert. So lag der Anteil an FIGO 3-4 Stadien in einer Studie aus Uganda im Jahre 2016 bei 66%[47]. Im Gegensatz hierzu wurden in den Jahren 2011 bis 2016 in Massachusetts (Vereinigte Staaten von Amerika) nur 13,7% der Zervixkarzinompatient*innen in einem FIGO Stadium 3-4 diagnostiziert[48]. Die hohen Stadien bei Diagnosestellung und der limitierte Zugang zu onkologischen Therapieoptionen in LMICs haben im Vergleich zu Daten aus HICs stark nachteilige Auswirkungen auf das Überleben der Patient*innen. Der CONCORD-2-Studie zufolge lag die 5-Jahres-Überlebensrate in dem Zeitraum zwischen 2005-2009 global gesehen in 7 Ländern bei ≥70%, in 34 Ländern zwischen 60-69% und in weiteren 20 Ländern bei ≤60%. Die niedrigsten Überlebensraten ließen sich in den meisten Ländern SSA's finden[49].

1.6 Zielstellung

Hauptgegenstand dieser Arbeit ist die Beschreibung der onkologischen Gesundheitsversorgung in SSA mit dem Fokus auf Addis Abeba (Äthiopien). Es gibt zum heutigen Zeitpunkt viele Studien, die auf die stetig steigenden Tumorinzidenzen und die mangelnde gesundheitliche Infrastruktur in SSA aufmerksam machen. Jedoch gibt es zum Zeitpunkt der Schriftlegung dieser Arbeit keine Daten über die populationsbezogene onkologische Versorgung von Patient*innen in SSA, die über eine Behandlungseinrichtung an ihrem Wohnort verfügen.

In der ersten hier vorliegenden Studie[50] haben wir die onkologische Versorgung derjenigen Patient*innen näher beleuchtet, welche in den ersten drei Monaten der Jahre 2012 und 2014 die Erstdiagnose ihrer malignen Erkrankung erhalten haben. Wir haben uns in dieser 2015

durchgeführten retrospektiven Auswertung von Krankenakten der Frage gewidmet, wie lange Patient*innen, die eine Chemotherapie bzw. Strahlentherapie erhalten haben, auf ihren Therapiebeginn warten mussten und zudem, wie vollständig die empfohlene Therapie verabreicht worden ist.

Darüber hinaus sind wir in unserer multinationalen Studie[51] der Frage nachgegangen, wie leitlinienadhärent Zervixkarzinompatientinnen, die zwischen 2010 und 2016 in acht verschiedenen Ländern SSA's diagnostiziert wurden, behandelt worden sind und wie sich der Zusammenhang zwischen Leitlinienadhärenz und Überleben dargestellt hat.

Innerhalb dieses Manuskriptes habe ich mich auf die Ausführung der eben genannten Studien konzentriert. Die von mir mitverfassten Studien zum Non-Hodgkin-Lymphom (NHL) sowie zum Prostatakarzinom werden innerhalb der vorliegenden Arbeit nicht behandelt.

Alle vier international veröffentlichten Studien eint das Ziel, die globale Aufmerksamkeit auf die defizitäre medizinische Versorgung onkologischer Patient*innen in SSA zu lenken und somit einen gesundheitspolitischen Wandel voranzutreiben. Wissenschaftliche Forschungsergebnisse im Gesundheitssystem sind für politische Entscheidungsträger eine essentielle Informationsgrundlage auf deren Basis Veränderungen möglich werden[52].

2 Diskussion

2.1 Eine populationsbezogene Kohortenstudie zur onkologischen Therapie in Addis Abeba, Äthiopien

2.1.1 Patient*innenkohorte

Der Großteil unserer Kohorte (74,8%) war zum Zeitpunkt der Diagnosestellung jünger als 60 Jahre alt. Zahlreiche Studien haben bereits über große internationale Altersunterschiede bei der Diagnosestellung maligner Erkrankungen berichtet[53]. So liegt das mediane Alter von Mammakarzinompatientinnen in der westlichen Welt bei 60-70 Jahren, wohingegen Frauen in afrikanischen Ländern im Mittel 45 Jahre alt sind[18,54]. Die Gründe für diesen internationalen Altersunterschied sind am ehesten Ausdruck der verschiedenartigen Altersstrukturen der Populationen[55]. Das vergleichsweise junge Alter bei der Diagnosestellung einer malignen Erkrankung in Ländern des globalen Südens bringt erhebliche ökonomische wie auch soziale Konsequenzen für die im Todesfall zurückgelassenen Kinder und Familien mit sich. Insbesondere Frauen tragen einen Großteil der gesellschaftlichen Arbeit. Sie haben Schlüsselrollen in der Sozialisation, der Bildung und in der Gesundheit der Kinder inne und ihr frühzeitiger und darüber hinaus häufig vermeidbarer Tod bringt komplexe und kaum überschaubare Folgen für die jeweilige Gesellschaft mit sich[56].

Der Großteil unserer Kohorte (69,9%) befand sich in einem fortgeschrittenen Tumorstadium (Stadium 3 oder 4). Dieses Ergebnis ist vergleichbar mit Studien aus anderen Ländern SSA‘s. So wurden 67,7% der Mammakarzinompatient*innen in Nigeria[57] und 71% der Mammakarzinompatient*innen in Äthiopien[54] in einem fortgeschrittenen Tumorstadium diagnostiziert.

2.1.2 Palliative Versorgung

Durch den großen Anteil fortgeschrittener Tumorstadien spielt die Palliativmedizin insbesondere in LMICs eine wichtige Rolle. Global gesehen erhalten lediglich 14% der Patient*innen, die eine palliative Behandlung benötigen, eine adäquate Therapie. Vor allem in LMICs gibt es einen großen ungedeckten Bedarf an palliativtherapeutischen Maßnahmen. So weisen diese Länder einen 1000-fach geringeren Verbrauch an Schmerzmitteln auf verglichen mit HICs[58]. In unserer Studie hat nur ein Drittel (31,6%) der Patient*innen, die sich im Stadium 4 ihrer malignen Erkrankung befanden, mindestens einmal im Dokumentationsverlauf ein Opiat entsprechend der Stufe 3 des WHO-Stufenschema‘s erhalten. Eine unzureichende Palliation kann dramatische Folgen für die Patient*innen und deren Angehörige mit sich bringen; das Verhindern von unnötigem Leid ist eine ethische Pflicht einer jeden Gesellschaft[59].

2.1.3 Wartezeiten für Chemo- und Strahlentherapie

Die mediane Wartezeit für eine chemotherapeutische Behandlung lag in unserer Kohorte für diejenigen Patient*innen, die auch tatsächlich einer Therapie zugeführt worden sind, bei 2,1 Monaten und die mediane Wartezeit für eine strahlentherapeutische Behandlung lag bei 6,9 Monaten. Einer im Jahre 2015 publizierten Metaanalyse von über 200 Studienergebnissen zufolge war für einen Großteil der Tumorentitäten ein kürzeres Zeitintervall zwischen Symptombeginn und Tumordiagnose mit einem früheren Tumorstadium, einem besseren Überleben und einer höheren Lebensqualität verbunden[60]. Dies gilt insbesondere für das Überleben beim Mammakarzinom, Kolonkarzinom und den Kopf- und Hals-Karzinomen; Tumorentitäten mit einer hohen Inzidenz in unserer Studie wie auch in anderen Ländern SSA's.

Jensen et al. zufolge hat sich das Tumorgesamtvolumen bei Karzinomen des Kopf-Hals-Bereiches nach einer medianen Zeit von 99 Tagen verdoppelt. 50% der besonders aggressiven Tumore haben sich in nur 30 Tagen verdoppelt[61]. Waaijer et al. kamen zu ähnlichen Ergebnissen: Die mediane Zeit bis zur Tumorverdopplung bei Oropharynxkarzinompatient*innen betrug 96 Tage. Während der medianen Wartezeit auf die Strahlentherapie von 56 Tagen vergrößerte sich die Tumormasse um 70% und die erwartete Therapieerfolgswahrscheinlichkeit sank von 63-66% auf nur 47%[62]. Im Jahre 2008 haben Chen et al. eine systematische Auswertung einiger Studien über den Zusammenhang zwischen der Wartezeit bis zur Strahlentherapie und dem klinischen Outcome publiziert. Der Studie zufolge ist eine steigende Wartezeit mit einem deutlich höheren lokalen Therapieversagen assoziiert. Das relative Risiko für das Therapieversagen betrug 1,15 pro Monat und das relative Mortalitätsrisiko 1,16 pro Monat[63]. Auf unsere Studie bezogen bedeutet dies bei einer medianen Wartezeit von 6,9 Monaten für eine Strahlentherapie ein relatives Risiko für ein Therapieversagen von 2,62 und ein relatives Mortalitätsrisiko von 2,78. Die von uns ermittelte mediane Wartezeit für eine strahlentherapeutische Behandlung ist vergleichbar mit einer Studie aus Kamerun. In dieser Studie mussten 69% der Mammakarzinompatient*innen länger als 6 Monate auf ihre strahlentherapeutische Behandlung warten[64].

2.1.4 Vollständigkeit der chemotherapeutischen Behandlung

Die fünf am häufigsten diagnostizierten Tumorentitäten, die lokaler Leitlinien zufolge eine chemotherapeutische Behandlung benötigten, waren das Mamma-, Lungen-, kolorektale und Ovarialkarzinom sowie das NHL. Die Vollständigkeit einer chemotherapeutischen Behandlung stand in unserer Kohorte in einem Zusammenhang mit der Tumorentität sowie mit dem Tumorstadium. So haben ambulant geführte Patient*innen und Patient*innen in weniger fortgeschrittenen Tumorstadien zu einem höheren Anteil eine vollständige Chemotherapie erhalten als Patient*innen, die sich in weiter fortgeschrittenen Tumorstadien befanden sowie derjenigen, die eine stationäre Behandlung benötigten. Auch Menon et al. konnten zeigen, dass

die Wahrscheinlichkeit, dass NHL-Patient*innen in Uganda die empfohlene Chemotherapie vollständig erhielten umso höher ausfiel, je niedriger das Tumorstadium war[65].

In unserer Kohorte wurden unter denjenigen Patient*innen, die eine Chemotherapie erhalten sollten, 54,1% vollständig behandelt. Lediglich 10% der Patient*innen haben eine unvollständige Behandlung von ≤85% erhalten und bei 35,9% der Patient*innen wurde keine Chemotherapie initiiert, obwohl laut lokaler Leitlinie eine Chemotherapie indiziert war. Die Gründe für eine fehlende Behandlung in unserer Kohorte sind uns nicht bekannt. Der geringe Anteil (10%) an Patient*innen mit unvollständigen Behandlungszyklen spricht aber für eine gute Patient*innenadhärenz nach begonnener Therapie. Mehrfach in der Literatur genannte Gründe einer abgelehnten bzw. einer frühzeitig beendeten Chemotherapie sind Nebenwirkungen der Behandlung wie Haarverlust, Übelkeit, Erbrechen und eine mögliche Infertilität, welche kulturell von vielen Patient*innen nicht in Kauf genommen wird[66]. Supportive Therapien sind in SSA nur dürftig verbreitet und so erscheint es plausibel, dass die genannten Nebenwirkungen einen Grund für Behandler*innen und Patient*innen darstellen, die indizierte Chemotherapie nicht fortzusetzen bzw. nicht zu beginnen[28].

Eine in Nigeria durchgeführte Studie kam zu dem Ergebnis, dass einer der Hauptgründe für einen Chemotherapieabbruch bei Mammakarzinompatient*innen ein subjektives Wohlbefinden nach begonnener Therapie war und damit einhergehend die Vorstellung, dass die bisherige Behandlung ausreichend gewirkt habe[67]. Nur durch eine ausführliche Aufklärung können die betroffenen Menschen über die Ernsthaftigkeit ihrer malignen Erkrankung und die lebensrettenden Möglichkeiten onkologischer Therapien informiert werden und soziale und kulturelle Stigmata maligner Erkrankungen abbauen.

Für eine sichere und für Patient*innen tolerierbare Chemotherapie ist es in LMICs von enormer Bedeutung, mehr ärztliches und pflegerisches Personal auszubilden. Strukturierte onkologische Ausbildungsprogramme sind unabdingbar, um die Qualität onkologischer Therapien zu verbessern und die Adhärenz und somit das Outcome der Patient*innen positiv zu beeinflussen[68]. Eine Studie, welche die globale Verfügbarkeit von Onkolog*innen untersucht hat, kam zu dem Ergebnis, dass in Äthiopien durchschnittlich ein*e Onkolog*in für die Behandlung von 10.167 malignen Erkrankungen zur Verfügung steht. Global gesehen stellt das Verhältnis an vorhandenen Onkolog*innen in Äthiopien bezogen auf die Bevölkerungszahl einen der niedrigsten Werte dar. Im Vergleich dazu ist das Verhältnis in den Vereinigten Staaten von Amerika 1:325[69].

2.1.5 Vollständigkeit der strahlentherapeutischen Behandlung

Eine unvollständige strahlentherapeutische Behandlung ist in SSA ein häufiges Phänomen. So können beispielsweise durch die häufigen Behandlungseinheiten die regelmäßigen Fahrten in die

Einrichtung zu erheblichen finanziellen Ausgaben führen. Auch die finanzielle Beteiligung an den Behandlungskosten führt in vielen Fällen zu einer Nonadhärenz[70].

Die vier am häufigsten diagnostizierten Tumorentitäten, die lokalen Leitlinien zur Folge eine strahlentherapeutische Behandlung benötigten, waren das Mamma-, Rektum-, Zervix- sowie die Kopf- und Halskarzinome. In dieser Kohorte haben 24,5% der Patient*innen eine vollständige Bestrahlung erhalten. Lediglich 2,1% der Patient*innen haben eine unvollständige Behandlung von ≤85% erhalten, was für eine sehr gute Therapieadhärenz nach initiierter Therapie spricht. Etwa zwei Drittel (61,9%) unserer Kohorte hat trotz bestehender Indikation keine strahlentherapeutische Behandlung erhalten. Die Gründe für die Nichtbehandlung sind uns nicht bekannt und können nur vermutet werden. Aufgrund der im Studienzeitraum vorhandenen sehr limitierten Strahlentherapiekapazität von einem Bestrahlungsgerät im gesamten Land sowie der in unserer Studie ermittelten medianen Wartezeit von 6,9 Monaten gehen wir am ehesten davon aus, dass die vorhandene Infrastruktur für die strahlentherapeutische Behandlung von allen Patient*innen nicht ausreichend gegeben war.

Ferner müssen auch andere Gründe in Betracht gezogen werden. Onkologische Behandlungen sind in SSA häufig finanziell besser gestellten Patient*innen vorbehalten. Eine große Querschnittsstudie aus Argentinien zeigte, dass Frauen, die an einem Zervixkarzinom erkrankt waren, relevante sozioökonomische Einbußen erlitten. Dies wiederum hatte einen negativen Einfluss auf die Strahlentherapieadhärenz und das, obwohl 96% der Kohorte die Kosten der Strahlentherapie nicht selber zahlen musste, da diese von den Krankenhäusern oder den Krankenversicherungen getragen wurden[71]. Diese im Jahre 2007 erschienene Studie bezieht sich auf ein Land mit mittlerem Einkommen und einem gut ausgebauten Gesundheitssystem, zu dem die meisten Menschen einen kostenlosen Zugang haben. Die wirtschaftlichen und sozialen Auswirkungen einer strahlentherapeutischen Behandlung müssten im subsaharischen Kontext ebenso dringend untersucht werden.

2.2 Das Zervixkarzinom in SSA: Eine multinationale populationsbezogene Kohortenstudie zur Therapieleitlinie und Leitlinienadhärenz

2.2.1 Therapie und Leitlinienadhärenz

Der Wohnort sowie der sozioökonomische Hintergrund sind entscheidende Risikofaktoren dafür, welche maligne Erkrankung Menschen entwickeln, in welchem Tumorstadium die Person erstmalig den Kontakt zum Gesundheitssystem sucht und ob sie Zugang zu finanziell tragbarer und qualitativ hochwertiger Diagnostik sowie Therapie erhält. Alarmierend ist dies insbesondere für Zervixkarzinompatient*innen, da 85% der global erfassten Erstdiagnosen und 87% der Todesfälle in LMICs registriert werden[39]. Es gibt zahlreiche Versuche, dieses Ungleichgewicht

zu beheben. In Äthiopien besteht beispielsweise seit 2015 ein nationales Zervixkarzinom-Screeningprogramm, basierend auf dem Essigsäuretest und der anschließenden Kryotherapie von essigweißen Läsionen. Bisher haben nur wenige Krankenhäuser dieses Screeningprogramm implementiert[72]. Auch wird diese Behandlungsmethode von vielen Frauen aufgrund einer fehlenden Akzeptanz nicht in Anspruch genommen und so zeigen Studien aus verschiedenen Gegenden Äthiopiens, dass lediglich 2-10% der Frauen, die Anspruch auf eine Zervixkarzinom-Screeninguntersuchung hätten, diese auch tatsächlich wahrnehmen[73].

Drastisch hat sich die onkologische Versorgungssituation der Zervixkarzinompatient*innen in unserer Studie gezeigt: Für mehr als die Hälfte (n=353) unserer Kohorte ließ sich keinerlei Dokumentation über eine onkologische Behandlung ausfindig machen und im ungünstigsten Falle haben die Patient*innen diese auch nicht erhalten. Weiterhin hat nur ein Drittel der verbleibenden Hälfte (n=100) eine Therapie mit einem kurativen Potential erhalten. Hierbei gab es große internationale Unterschiede abhängig von der Verfügbarkeit einer perkutanen Strahlentherapie im jeweiligen Registergebiet. So variierte die Rate an Behandlungen mit kurativem Potential zwischen 4% (n=5) in Mosambik, wo im Untersuchungszeitraum keinerlei Bestrahlungsoption für die Patient*innen bestand und 49% (n=29) in Kenia; einem Land mit vergleichsweise gut ausgebildeter Strahlentherapieinfrastruktur (Verhältnis von Bestrahlungsgerät zur Bevölkerungszahl: 1:538.462)[33].

In Addis Abeba haben 46,4% (n=13) der Patient*innen mit vorhandenen Therapiedaten eine onkologische Therapie mit kurativem Potential erhalten. Hierbei wiederum handelt es sich in 23,1% der Fälle (n=3) um eine strikt leitliniengerechte Therapie, in 7,7% der Fälle (n=1) um geringe Abweichungen einer leitliniengerechten Therapie und im Großteil der Fälle (69,2%, n=9) um starke Abweichungen einer leitliniengerechten Therapie. Gesetzt den Fall, Patient*innen ohne auffindbare Krankenakte und ohne dokumentierte Therapiedaten haben auch keine onkologische Therapie in Addis Abeba erhalten, so sinkt der Anteil an Patient*innen, die eine potentiell kurativ onkologische Therapie erhalten haben von 46,4% auf nur 16,8%.

2.2.2 Zusammenhang zwischen Leitlinienadhärenz und Überleben

Die geringe Leitlinienadhärenz war mit einem schlechteren Überleben vergesellschaftet. Die ein-drei- und fünf-Jahres-Überlebenswahrscheinlichkeit lag in unserer gesamten Kohorte bei 75,6%, 42,4% und 28,7%. Diese Zahlen sind vergleichbar mit Studien aus Uganda[74] und Zimbabwe[75] und liegen weit unter den Überlebenswahrscheinlichkeiten die Studien aus HICs berichtet haben. So lag beispielsweise die altersstandardisierte fünf-Jahres-Überlebenswahrscheinlichkeit in den USA zwischen 2007-2013 bei 67,1%.[76] Der Zusammenhang zwischen Leitlinienadhärenz der Therapie und Überleben ähnelte einem Dosis-Wirkungs-Effekt. So sank die Überlebenswahrscheinlichkeit mit zunehmend geringerer Leitlinienadhärenz. Dieser Effekt

reichte von einer 1,7-fachen Hazard Ratio bei geringen Abweichungen der Leitlinienadhärenz bis zu einer 9-fachen Hazard Ratio bei keinerlei erhaltener onkologischer Behandlung. Diese Zahlen sind vergleichbar mit einer australischen Studie. In dieser Studie hatte eine Leitlinienadhärenz der Therapie bei Patientinnen, die im Zeitraum zwischen 2005-2011 mit dem Zervixkarzinom in den FIGO Stadien 1 und 2 diagnostiziert wurden, ebenso einen direkten positiven Einfluss auf das Überleben[77].

Frühe Tumorstadien zum Zeitpunkt der Erstvorstellung sind in unserer, wie auch in anderen Studien, mit einem besseren Überleben vergesellschaftet. Zudem haben wir in unserer Kohorte bei Patient*innen im FIGO Stadium 1 einen weitaus größeren Anteil von 53% an strikter Leitlinienadhärenz beobachten können als in den FIGO Stadien 2 (12%) und 3 (3%). Dies sollte politische Entscheidungsträger dazu veranlassen, einen besonderen Fokus auf die Früherkennung von Zervixkarzinomen zu legen.

2.3 Ausblick

Trotz der defizitären Versorgungssituation onkologischer Patient*innen in SSA gibt es vielversprechende Entwicklungen hinsichtlich einer Verbesserung der Behandlungsinfrastruktur. Die äthiopische Regierung hat beispielsweise im Jahre 2015 - in Anbetracht der steigenden Inzidenzen maligner Erkrankungen - einen nationalen Plan zur Bekämpfung von Tumorerkrankungen verabschiedet. Dieser Plan beinhaltet ambitionierte Vorhaben wie die Verbreitung präventiver Maßnahmen, die Ausweitung von Screeningverfahren für eine frühzeitige Diagnosestellung sowie die Bereitstellung grundlegender onkologischer Behandlungsoptionen wie der Chirurgie, Chemotherapie, Strahlentherapie, Hormontherapie und eine Verbesserung der palliativen Versorgung an sechs weiteren Standorten[72].

Onkologische Therapien sind in SSA häufig finanziell besser gestellten Patient*innen vorbehalten. Staatliche Versicherungsprogramme können den Zugang zum Gesundheitssystem sowie das Überleben onkologischer Patient*innen verbessern[78]. Die baldige Umsetzung politischer Bestrebungen in Äthiopien eine nationale Krankenversicherung einzuführen wäre ein wichtiger Schritt in Richtung einer Verbesserung der aktuellen onkologischen Versorgungsstruktur[79].

2.4 Limitationen und Stärken

Trotz intensiver Recherche konnten wir nur die Hälfte (51,2%) der im Krebsregister gemeldeten Fälle in der ersten[50] und zwei Drittel (63%) in der zweiten der beiden Studien[51] ausfindig machen. Wir müssen davon ausgehen, dass die Mehrzahl der Patient*innen, deren Akte nicht auffindbar

war, wahrscheinlich keinerlei onkologische Therapie erhalten hat und somit keine klinischen Akten initiiert wurden.

Durch unsere Studien wurden nur Patient*innen erfasst, die Zugang zu einer diagnostischen Abklärung hatten. Onkologische Patient*innen, die vor Diagnosestellung ihrer malignen Erkrankung verstorben sind oder keine professionelle Anlaufstelle kontaktiert haben, sind in unseren Studien nicht repräsentiert. Wir gehen davon aus, dass die meisten Patient*innen in den Hauptstädten am ehesten die Chance haben, eine Gesundheitseinrichtung aufzusuchen. Für Menschen aus ländlichen Gegenden sind die Therapieoptionen deutlich eingeschränkter[19]. Unsere Studien liefern Einblicke in wichtige Aspekte der urbanen onkologischen Versorgung in SSA, sollten jedoch zwingend Studien aus dem ruralen Raum SSA's nach sich ziehen. Weiterhin lagen uns aufgrund des retrospektiven Charakters der Studie sowie der teils lückenhaften Dokumentation keine Informationen zu den Gründen einer unvollständigen Behandlung beziehungsweise einer Verzögerung des Therapiebeginns vor. Die Gründe sind sicherlich multifaktoriell. Aufgrund der kritischen, insbesondere strahlentherapeutischen Versorgungsstruktur gehen wir aber am ehesten von einer institutionellen Verzögerung der onkologischen Behandlung aus.

Die vorliegenden beiden Studien liefern grundlegende Informationen zur Behandlung onkologischer Patient*innen in SSA. Unseren Recherchen zufolge sind sie in den genannten Ländern die ersten populationsbezogenen Studien, die sich mit den Wartezeiten, der Vollständigkeit von onkologischen Therapien, der Leitlinienadhärenz und dessen Auswirkungen auf das Überleben auseinandersetzen und somit einen wichtigen gesundheitspolitischen Beitrag leisten.

2.5 Fazit

Die Ergebnisse unserer beiden Studien zeigen, dass ein Großteil der Tumorpatient*innen in SSA eine suboptimale oder keine onkologische Therapie erhalten hat. Häufig sahen sich Patient*innen mit langen Wartezeiten konfrontiert und die Patient*innen haben die empfohlene Therapie nur unvollständig oder überhaupt nicht erhalten. Zukünftig sollten detaillierte Gründe erfasst werden um mögliche Verbesserungen zu realisieren. Durch eine steigende Lebenserwartung wird die Anzahl onkologischer Patient*innen weiter zunehmen. Die betroffenen Gesundheitssysteme müssen sich dieser Herausforderung stellen und die onkologische Versorgungsstruktur ausbauen. Die Ergebnisse unserer Studien unterstreichen insbesondere den akuten Bedarf an zusätzlichen Bestrahlungsgeräten. Weiterhin gibt es einen hohen Bedarf an einer verbesserten chemotherapeutischen sowie palliativen Versorgung.

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4 Thesen

1. Die Altersstruktur Äthiopiens spiegelt sich in unserer Studie wider: ein Großteil (74,8%) unserer Kohorte in Addis Abeba war zum Diagnosezeitpunkt jünger als 60 Jahre alt.
2. Mehr als zwei Drittel (69,9%) unserer Kohorte in Addis Abeba wurde in einem fortgeschrittenen Tumorstadium (Stadium 3 oder 4) diagnostiziert, so dass ein besonderer Fokus auf Aufklärungskampagnen sowie Screening-Maßnahmen sinnvoll erscheint, um Patient*innen frühzeitiger eine onkologischen Therapie zu ermöglichen.
3. Mehr als die Hälfte (54,1%) der onkologischen Patient*innen in Addis Abeba mit einer der fünf am häufigsten diagnostizierten Tumorentitäten, welche eine Chemotherapie benötigten, hat eine vollständige Behandlung erhalten.
4. Lediglich ein Viertel (24,5%) der onkologischen Patient*innen in Addis Abeba mit einer der vier am häufigsten diagnostizierten Tumorentitäten, welche eine Strahlentherapie benötigten, hat eine vollständige Behandlung erhalten.
5. In Addis Abeba lag die mediane Wartezeit für eine chemotherapeutische Behandlung für diejenigen Patient*innen, die einer Therapie zugeführt worden sind, bei 2,1 Monaten, was einen adäquaten Therapiebeginn zumindest für einen relevanten Teil der Patient*innen zeigt.
6. In Addis Abeba lag die mediane Wartezeit für eine strahlentherapeutische Behandlung für diejenigen Patient*innen, die einer Therapie zugeführt worden sind, bei 6,9 Monaten, so dass der dringende Bedarf an weiteren Bestrahlungseinheiten deutlich wird.
7. Der geringe Anteil an unvollständigen Behandlungszyklen in Addis Abeba in der chemotherapeutischen (10,0%) sowie in der strahlentherapeutischen (2,1%) Versorgung spricht für eine sehr gute Patient*innenadhärenz.
8. Der Anteil an Therapieansätzen mit kurativem Potential bei Zervixkarzinom-Patientinnen lag mit 16,8% in Addis Abeba im Vergleich zu Daten aus acht anderen populationsbezogenen Registern Subsahara-Afrika's (4%-49%) im mittleren Bereich.
9. Bei einem Großteil (69,2%) der Zervixkarzinom-Patientinnen in Addis Abeba, die einer onkologischen Therapie mit kurativem Potential zugeführt wurden, handelte es sich um Therapieansätze mit starken Abweichungen der Leitlinienadhärenz. Eine Abnahme der Leitlinienadhärenz war in unserer Studie mit einer geringeren Überlebenswahrscheinlichkeit assoziiert.

Publikationsteil

Publikation 1:

Feuchtner J, Mathewos A, Solomon A, Timotewos G, Aynalem A, Wondemagegnehu T, Gebremedhin A, Adugna F, Griesel M, Wienke A, Addissie A, Jemal A, Kantelhardt EJ. Addis Ababa population-based pattern of cancer therapy, Ethiopia. PLoS One. 2019 Sep 19;14(9):e0219519. doi: 10.1371/journal.pone.0219519. PMID: 31536505; PMCID: PMC6752935.

Mein Beitrag als Autorin:

Ich war maßgeblich beteiligt an der Erstellung eines Studienkonzeptes, eines Designs sowie der Planung der Studiendurchführung. Anschließend habe ich im Rahmen eines 6-monatigen Aufenthaltes in Addis Abeba (Äthiopien) die Arbeit des lokalen Krebsregistern (AACCR) kennengelernt und nach einer Einarbeitung eigenverantwortlich die Daten aus den papierbasierten Krankenhausakten exzerpiert und in eine Datenbank eingepflegt. Ich war maßgeblich an der Analyse der Daten und deren Interpretation beteiligt und ich schrieb federführend das Manuskript der vorliegenden Publikation.

Publikation 2:

Griesel M, Seraphin TP, Mezger NCS, Hämmerl L, **Feuchtner J,** Joko-Fru WY, Sengayi-Muchengeti M, Liu B, Vuma S, Korir A, Chesumbai GC, Nambooze S, Lorenzoni CF, Akele-Akpo MT, Ayemou A, Traoré CB, Wondemagegnehu T, Wienke A, Thomssen C, Parkin DM, Jemal A, Kantelhardt EJ. Cervical Cancer in Sub-Saharan Africa: A Multinational Population-Based Cohort Study of Care and Guideline Adherence. Oncologist. 2021 May;26(5):e807-e816. doi: 10.1002/onco.13718. Epub 2021 Mar 10. PMID: 33565668; PMCID: PMC8100544.

Mein Beitrag als Autorin:

Im Rahmen dieser Publikation habe ich am Studienkonzept sowie am Studiendesign und der Durchführung mitgewirkt. Die von mir in Addis Abeba gesammelten Daten zum Zervixkarzinom wurden innerhalb dieser Studie für weiterführende Analysen verwendet. Die Studienergebnisse habe ich im Rahmen der FIDE- Jahrestagung (Frauengesundheit in der Entwicklungszusammenarbeit) im Jahre 2019 präsentiert und diskutiert. Gemeinsam mit den Koautor*innen kommentierte und revidierte ich die Manuskriptentwürfe des Erstautors.

Publikationen 3 und 4

Mezger NCS, **Feuchtner J**, Griesel M, Hämmerl L, Seraphin TP, Zietsman A, Péko JF, Tadesse F, Buziba NG, Wabinga H, Nyanchama M, Borok MZ, Kéita M, N'da G, Lorenzoni CF, Akele-Akpo MT, Gottschick C, Binder M, Mezger J, Jemal A, Parkin DM, Wickenhauser C, Kantelhardt EJ. Clinical presentation and diagnosis of adult patients with non-Hodgkin lymphoma in Sub-Saharan Africa. Br J Haematol. 2020 Jul;190(2):209-221. doi: 10.1111/bjh.16575. Epub 2020 Mar 17. PMID: 32181503.

Seraphin TP, Joko-Fru WY, Hämmerl L, Griesel M, Mezger NCS, **Feuchtner JC**, Adoubi I, Egué MD, Okerosi N, Wabinga H, Hansen R, Vuma S, Lorenzoni C, Coulibaly B, Odzebe SW, Buziba NG, Aynalem A, Liu B, Medenwald D, Mikolajczyk RT, Efstathiou JA, Parkin DM, Jemal A, Kantelhardt EJ. Presentation, patterns of care, and outcomes of patients with prostate cancer in sub-Saharan Africa: A population-based registry study. Cancer. 2021 Jul 30. doi: 10.1002/cncr.33818. Epub ahead of print. PMID: 34328216.

Mein Beitrag als Autorin:

Innerhalb dieser beiden Studien war ich beteiligt an der Entwicklung eines Konzeptes, eines Designs sowie in der Planung der Sudiendurchführung. Wie schon in Publikation 2 beschrieben, habe ich die durch mich in Addis Abeba gesammelten Daten (in diesem Fall zum NHL sowie zum Prostatakarzinom) zur weiteren Analyse zur Verfügung gestellt. Gemeinsam mit den Koautor*innen habe ich die Manuskriptentwürfe der Erstautoren kommentiert und revidiert.

Förderung im Rahmen meiner Promotion:

Während meines Auslandsaufenthaltes in Äthiopien habe ich ein Promotionsstipendium der Bayer-Stiftung erhalten. Zudem wurde die Promotion finanziell durch die AG FIDE e.V. gefördert.

PLOS ONE

RESEARCH ARTICLE

Addis Ababa population-based pattern of cancer therapy, Ethiopia

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Abstract

Cancer in Sub-Saharan Africa is becoming an important challenge for health services due to rising numbers of patients. In Addis Ababa with around 3.5 million inhabitants, more than 2000 cases are diagnosed annually. In this retrospective population-based cohort study we assessed completeness of and waiting time for cancer-therapy among patients registered in the Addis Ababa City Cancer Registry (AACCR), Ethiopia. Patient hospital files were retrieved to complete the data from AACCR. A total of 588 files were found (51% of those diagnosed from January to March 2012 and 2014). We analyzed completeness and waiting time of chemotherapy and radiotherapy; with completeness defined as ≥85% therapy received according to local guidelines. Analysis was done for the five most common cancer-types commonly treated with chemotherapy (breast, colorectal, non-Hodgkin's lymphoma, lung and ovarian) and the four most common cancer-types commonly treated with radiotherapy (breast, cervical, head and neck and rectal). In our study, half of the patients (54.1%) received adequately dosed chemotherapy and 24.5% of patients received adequately dosed radiotherapy. The median waiting time was 2.1 months (Range: 0 to 20.72) for chemotherapy and 7 months (Range: 0.17 to 21.8) for radiotherapy. This study underscores the need for health system measures to improve cancer-directed therapy in Ethiopia, especially concerning radiotherapy.

Introduction

Cancer in sub-Saharan Africa (SSA) is on the rise caused by a rapid population growth, higher life expectancy and adoption of unhealthy lifestyles [1], [2]. Africa's population is growing rapidly. According to UN estimates, the continent will double from 1.2 billion people in 2015 to 2.5 billion in 2050 [3], making its population the fastest growing worldwide with a shift towards an older age distribution [4]. This makes cancer a severe force to be reckoned with and a huge challenge for the health care systems of Africa.

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Competing interests: The authors have declared that no competing interests exist.

Cancer therapy options in most SSA countries are sparse and when available, they are unable to sufficiently serve patients'needs [5]. The Concord 2 study has shown that cancer survival rates differ significantly around the world, with Africa in last place for most types of cancer [6]. This striking fact is most likely due to late-stage presentation [7] and poor access to therapy [5]. Studies estimate that 80% of the 15.2 million new cancer cases in 2015 will need a surgical intervention at least once. Yet, only 25% of cancer patients worldwide and less than 5% in low-income countries get timely, affordable and safe surgery [8]. Cancer diagnoses in some SSA countries are often solely based on a clinical diagnosis not verified through biopsy, making cancer care an even more difficult task [9]. The use of adjuvant therapy in SSA has steadily increased in the past decades. Surgeons used to be the ones responsible for chemotherapy, but there has been a rise in the number of oncologists in the past years [10]- however still not enough to serve the increasing demand. The main obstacle to sufficient cancer chemotherapy is the availability and cost of chemotherapeutic agents. The use of generic drugs from Asia is common; patented drugs are often not affordable which can lead to chemo-morbidity due to different bio-equivalencies and efficacies [10]. Only 23 out of 52 countries in Africa have radiotherapy available, Southern and Northern Africa possessing 90% of the total machines available [11]. In this study, we aimed to describe pattern of therapy of individual cancer patients from Addis Ababa, Ethiopia. Roughly 81% of the 107 million Ethiopian population lives in rural areas, 3.5 million in Addis Ababa [12], [13]. There were 0.03 physicians for every 1000 people in 2016 compared to 3.7 in high-income European countries [14]. The Tikur Anbessa specialized hospital was Ethiopia's only center for cancer offering oncologic surgery, chemotherapy and radiotherapy with one cobalt-60 teletherapy machine. The hospital had a capacity of 600 beds; 18 beds were dedicated to cancer patients [15]. A study from 2006 estimated a demand of 85 additional radiotherapy-machines for Ethiopia and highlighted the tremendous health service deficit [16]. A total of just over 2000 new cancer cases were detected annually in the Addis Ababa population-based cancer registry (AACCR) [17], which was founded 2011. The AACCR data is the basis for the WHO Globocan estimations [18].

Little is known about pattern of cancer therapy in settings with limited resources such as Ethiopia. This study aims to provide an overview of cancer stages and therapy using individual patient data from the AACCR. A cohort from 2012 (longer follow-up, assumed more difficult to access) and a second cohort from 2014 (shorter follow-up, assumed easier to access) were chosen for data collection at the end of 2015 to assess feasibility of obtaining sufficient details of information. This data will be the basis to assess the unmet need for cancer treatment in Addis Ababa, Ethiopia.

Methods and materials

Study design

This retrospective population-based cohort study was conducted within the population-based AACCR.

Setting, participants and variables

AACCR actively collects all new cancer patients who are residents of Addis Ababa from 20 collaborating institutions (pathology, oncology and radiotherapy facilities). Basic information is documented; due to time constraints, details about therapy are not registered. All cancer patients registered in the AACCR between January 1st and March 31st of the years 2012 and 2014 were included in this study, thus assuming a random sample. Hospital files of the registered patients were retrieved between October 2015 and February 2016 to complete information on therapy.

Study size and bias

The original sample consisted of 1149 patients, registered by the AACCR. The tracing rate of the hospital files in the 1012 cohort was 48.4% and 62.4% in the 2014 cohort. A total of 44 patients had to be excluded due to primarily false registration (e.g. benign disease). The resulting study size consisted of 588 patients with information from files available (51.2% of the 1149 AACCR cases); the remaining 48.8% files were not retrieved.

To investigate selection bias of the study population, proportions of known characteristics were compared between the AACCR cohort and the study cohort.

We expected files from 2012 would possibly be more difficult to obtain compared to more recent files from 2014. In case the proportion of files detected as well as completeness of therapy did not differ much between the 2012 and 2014 cohort, we planned to combine both for analysis.

Staging

Tumors were classified according to the International Union for Cancer Control (UICC) [19] and assessed at time-point of diagnosis. Gynecologic tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) [20] and later converted to UICC-classification. In cases of missing stage-information and strong evidence of a metastatic disease (n = 23), these patients were staged as stage four.

Completeness of therapy

Chemotherapy and radiotherapy were assessed with respect to completeness of the original intended treatment plan irrespective of reason for discontinuation. Local, simplified oncological therapy guidelines were: breast cancer stages 2–4 chemotherapy, stage 1 chemotherapy in case of high risk features and stages 3–4 additional radiotherapy; cervical cancer stages 2–4 concurrent radio-chemotherapy; non-Hodgkin's lymphoma stages 2–4 chemotherapy; colon cancer stages 3–4 chemotherapy; lung cancer stages 2–4 chemotherapy; ovarian cancer stages 2–4 chemotherapy; head-and-neck cancer stages 2–4 concurrent radio-chemotherapy; and rectal cancer stages 2–4 concurrent radio-chemotherapy.

Complete chemotherapy was defined when patients received $\geq$85% of the intended cycles referring to a study showing a better 20 year relapse-free survival in breast cancer patients (52.3% compared to 31.5% relapse-free survival) [21]. We applied the same cut-off for completeness of radiotherapy. Local therapy plans differed from high-income countries due to lack of 3D radiation and limitations of the Cobalt-60 tele machine. Analysis on completeness of therapy was done for the five and four most common cancer types, wherever chemotherapy or radiotherapy applied.

Time to therapy

Time to therapy was calculated between date of therapy planning and initiation of therapy. Patients with unknown starting as well as ending date of therapy were not included (n = 67 chemotherapy and n = 50 radiotherapy). Patients booked for palliative hemostatic-radiotherapy were excluded, because they received an immediate emergency-radiation (e.g. massive cervical cancer bleeding). Furthermore, patients receiving radio-chemotherapy were excluded from analysis of waiting time for chemotherapy because time to treatment mainly depended on radiotherapy.

Statistical methods

Analysis was performed using SPSS Statistics, Version 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). We obtained ethical approval

(124/10/IM) from the Addis Ababa Medical Faculty Review Board and the Martin-Luther-University Halle Review Board. All data/samples were fully anonymized before accessed.

Results

A total of 588 patient files were analyzed. To assure a representative sample, frequency of cancer entities within those files retrieved were compared with those registered in AACCR (n = 1149). This comparison showed a similar distribution which supported our assumption of missing files at random. The 10 most common cancer types are described in Table 1.

The majority of patients (74.8%) were under the age of 60 years. More than two thirds (68.7%) were female. The largest group of patients with known performance status (24.1%) was lightly restricted by their disease (ECOG1). A high percentage of patients presented with a late stage 4 disease (38.8%) and a negligible proportion of cancer entities (2.0%) presented with stage 1. (See Table 2)

About two thirds (64.8%) of patients received their therapy in a governmental hospital. One fifth of the patient cohort never received any operation, chemotherapy or radiotherapy; the

Table 1. Clinical and pathological characteristics of the study population (subgroup of AACCR*) compared to the AACCR cohort.

		Study population Number [n]	Study population Proportion [%]	Number in AACCR [n]	Proportion in AACCR [%]
Total population		588	100	1149	100
Age (years)					
<30		83	14.1	182	15.8
30–39		113	19.2	210	18.3
40–49		131	22.3	226	19.7
50–59		113	19.2	229	19.9
60–69		86	14.6	177	15.4
≥70		62	10.6	125	10.9
Sex					
Female		404	68.7	764	66.5
Male		184	31.3	385	33.5
Type of hospital					
Governmental		381	64.8	730	63.5
Private		207	35.2	419	36.5
Cancer entity	ICD-10 Code				
Breast**	C50-X	165	28.1	244	21.2
Cervix	C53-X	51	8.7	117	10.2
Colorectal	C18-X-C20-X	45	7.7	79	6.9
Non-Hodgkin-lymphoma	C83-X	40	6.8	66	5.7
Lung	C34-X	28	4.8	26	2.3
Sarcoma	C49-X	26	4.4	42	3.7
Thyroid	C73-X	22	3.7	48	4.2
Ovary	C48-X	18	3.1	43	3.7
Cancer of unknown primary	C80-X	15	2.6	27	2.3
Esophagus	C15-X	15	2.6	31	2.7
Others	/	163	27.5	426	37.1

*AACCR: Addis Ababa City Cancer Registry.

**breast cancer in male [n = 8].

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Table 2. Patients characteristics and treatment received in the study cohort.

	Number [n]	Proportion [%]
ECOG* at time of presentation		
Fully active (ECOG 0)	20	3.4
Lightly restricted (ECOG1)	142	24.2
Unable to work (ECOG 2)	89	15.1
Limited self-care, >50% in bed (ECOG 3)	50	8.5
No self-care, bed bound (ECOG 4)	11	1.9
unknown ECOG	276	46.9
Stage at time of presentation		
Stage 1	12	2.0
Stage 2	58	9.9
Stage 3	75	12.7
Unknown, probably stage 2 or 3	215	36.6
Stage 4	228	38.8
Any therapy received (operation, chemotherapy, radiotherapy)		
yes	475	80.8
no	113	19.2
Operation received		
yes	306	52.0
no	282	48.0
Chemotherapy for patients in demand (top 5 cancer-entities)		
yes	187	64.0
no	84	28.8
unknown	21	7.2
Worst case scenario chemotherapy (top 5 cancer-entities)		
yes	187	32.0
no	397	68.0
Radiotherapy for patients in demand (top 4 cancer-entities)		
yes	50	26.6
no	138	73.4
Worst case scenario radiotherapy (top 4 cancer-entities)		
yes	50	13.3
no	326	86.7

*ECOG = Eastern Cooperative Oncology Group.

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majority (80.8%) received at least one therapeutic modality. One half (52%) of patients were operated for their primary tumor, and 54.1% of the whole patients cohort were treated with chemotherapy. One third (31.6%) of stage 4 cancer patients received a WHO-pain-ladder 3 medication.

As a worst case scenario, we assumed that no therapy was given to those patients whose file could not be traced. This estimated that 68.0% of the original AACCR cohort eligible for chemotherapy was not treated and 86.7% of the cohort eligible for radiotherapy was not treated.

Completeness of chemotherapy for eligible patients

There were 292 patients (49.7%) in our study-cohort who had one of the five most common cancer types treated with chemotherapy according to local guidelines: breast cancer (n = 165), colorectal cancer (n = 42), non-Hodgkin's lymphoma (n = 40), lung cancer (n = 28) and ovarian

cancer (n = 17). Half of these patients (54.1%/ n = 158) received complete therapy. Breast cancer patients most commonly completed chemotherapy (64.2% of all breast cancer cases n = 106). Once chemotherapy was started 9.9% (n = 29) of all patients did not receive complete treatment. This could be due to progression of the disease, side-effects, economic, logistic or other reasons (personal information). A minority (5.8%/ n = 17) of all eligible patients was booked for chemotherapy, but eventually did not start. The largest proportion of them suffered from cancer of the lung (14.3%/ n = 4) and colorectal cancer (14.3%/ n = 6). One quarter (22.9%/ n = 67) of the patients eligible had no planned chemotherapy. The largest proportion of these were among lung (39.3%/ n = 11),colorectal (35.7%/ n = 15) and ovarian cancer patients (23.5%/ n = 4) and smallest in breast cancer (18.2%/ n = 30) and non-Hodgkin's lymphoma (17.5%/ n = 7). 7.2% (n = 21) of patients had an unknown therapy status [Fig 1].

Completeness of radiotherapy

We found 188 patients (32.0% of the patients cohort) eligible for radiotherapy, of which breast cancer patients stages 3 and 4 were the majority (n = 103), followed by cervical stages 2–4 (n = 36), head-and-neck stages 3 and 4 (n = 33), and rectal cancer stages 2–4 (n = 16). One fourth (24.5%, n = 46) of these patients completed their prescribed dose of radiotherapy, with the proportions almost equally distributed among the entities. A very small patient group (2.1%, n = 4) received an incomplete radiotherapy of <85% of fractions, whereas a high

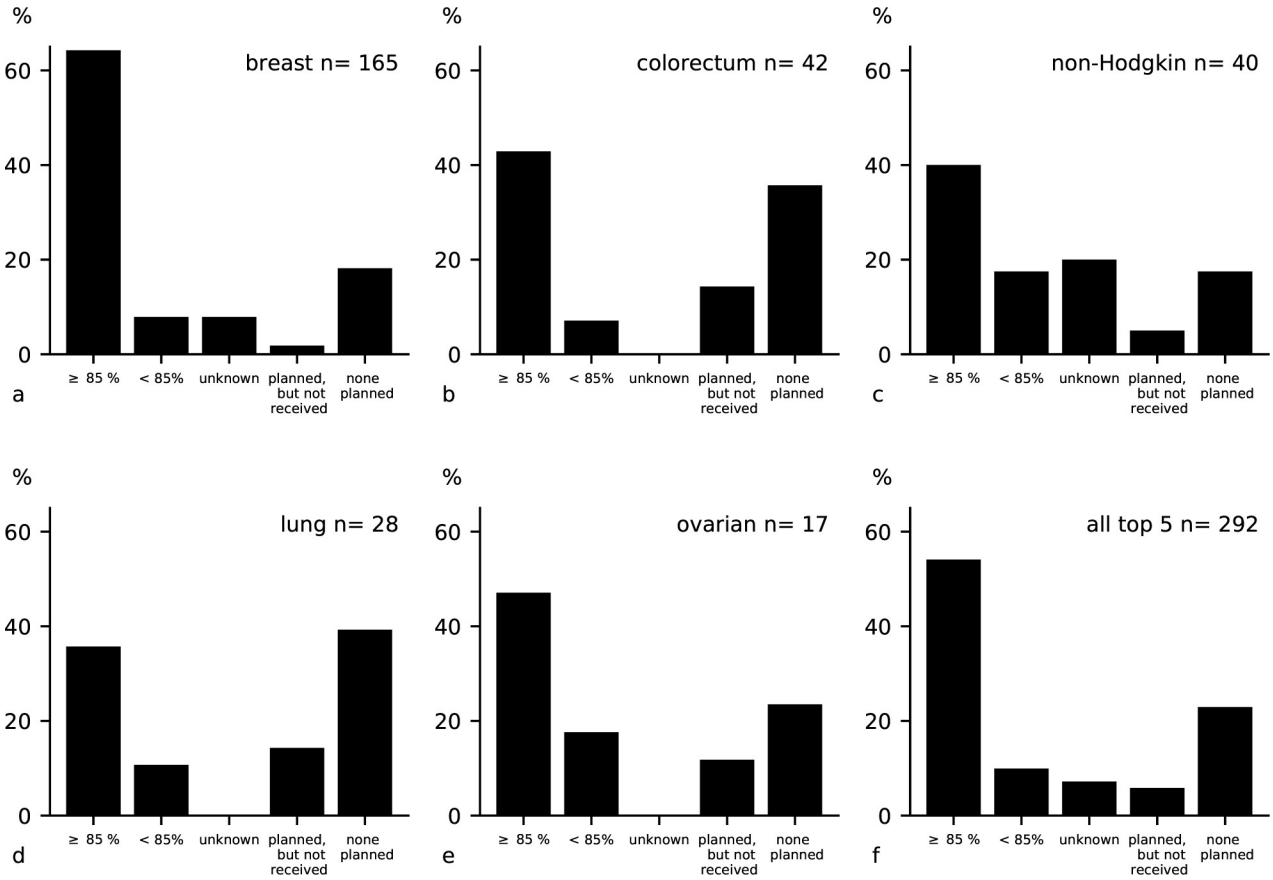

Fig 1. Completeness of chemotherapy according to local guidelines in top 5 cancer entities: (a) breast cancer stages 1–4; (b) colorectal cancer stages 3–4; (c) Non-Hodgkin's lymphoma stages 2–4; (d) lung cancer stages 2–4; (e) ovarian cancer stages 2–4; (f) all 5 cancer entities together.

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percentage of patients (23.9%, n = 45) never started the planned radiotherapy. Radiotherapy was not prescribed for a high proportion of patients (38.8%, n = 73), despite their registration and eligibility [Fig 2].

Waiting time

The median waiting time for the 253 chemotherapy patients was 2.1 months (Range: 0 to 20.72). Out of 100 radiotherapy/radiochemotherapy patients eligible we found a median waiting time of 6.9 months (Range: 0.17 to 21.8) [Fig 3].

The median waiting time until the start of any of those two therapy options was 2.2 months (Range: 0–20.72). The majority (n = 253) had chemotherapy as their primary treatment and a small proportion (n = 30) received radiotherapy only.

Discussion

In Addis Ababa about half of the eligible cancer patients received the planned chemotherapy within 6 months after diagnosis and about 25% received the planned radiotherapy within 12 months after diagnosis. Half of the patient cohort received oncologic surgery for their primary cancer.

We found a very young patient cohort mainly below the age of 60, consistent with the population structure of Ethiopia [22]. A high proportion presented with stage 4 diseases (38.8%)

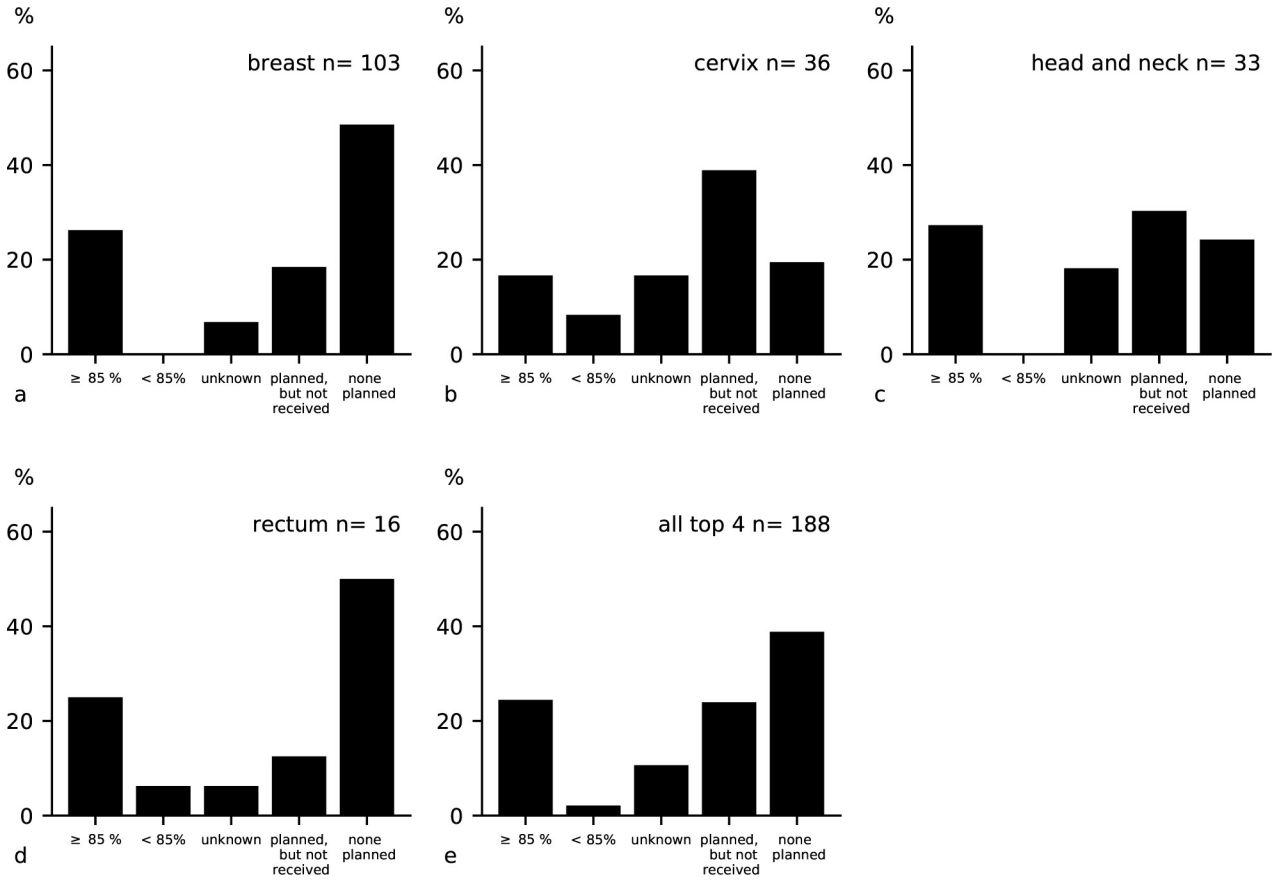

Fig 2. Completeness of radiotherapy according to local guidelines in top 4 cancer entities: (a) breast cancer stages 3 and 4; (b) cervical cancer stages 2–4 without single-shot; (c) head and neck cancer stages 2–4; (d) rectal cancer stages 2–4; (e) all 4 cancer entities together.

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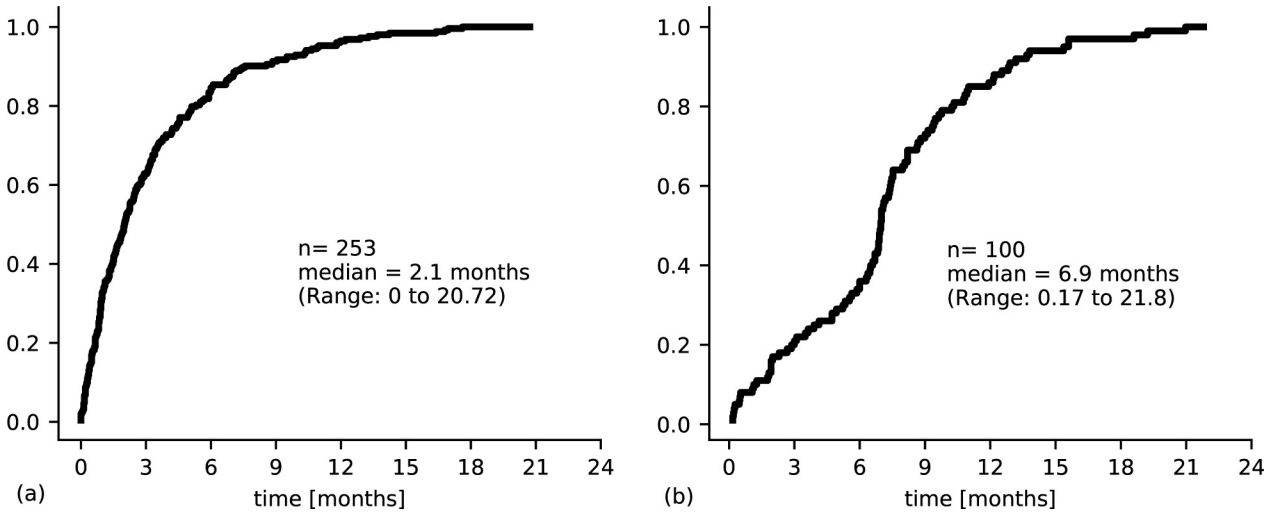

Fig 3. Cumulative probability of receiving chemotherapy (a) and radiotherapy (b) over time [in months].

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comparable with recent studies from Ethiopia showing 34.2% of cervical cancer patients [23] and 57–70.8% of breast cancer paients [24,25] presenting in advanced stages. A low level of cancer awareness, lack of screening programs [26], limited access to health-care institutions, poor financial situations and traditional medicine are often cited explanations in Africa [27], [28], [29]. Since pain is the most prevalent symptom in advanced cancer patients [30], we highlight an unmet need of treatment finding only one third receiving an adequate WHO-pain-ladder 3 medication [31].

Our findings of 2.2 months waiting time until the start of cancer therapy (essentially consisting of the time to chemotherapy) seems high but can still be compared to studies performed in other African settings: e.g. a 5 week median waiting time to cancer therapy in Ghana [32], 21.5 days to cancer therapy in Kenya [33], 1.3 months for breast cancer patients in Mali [34] and even 3 months to cancer therapy for patients in Botswana [35]. In contrast, patients in Germany wait 15 days until the start of cancer treatment [36].

A long waiting time for therapy and perceived inefficiency cause many patients to opt for alternative medicine in Ethiopia. Estimates suggest that more than 80% of health problems are treated by traditional health care practices, with cancer being among the top ten reasons [37].

Completeness of chemotherapy in our cohort was influenced by cancer stage and type. Early cancer stages 1 and 2 received complete chemotherapy according to guidelines (82.2%) more often than stage 3 cancer patients (67.3%). Breast cancer patients and non-Hodgkin's lymphoma patients also received adequate therapy more often. Out-patient service without competition for beds had been installed for these patients requiring chemotherapy only. In contrast, chemotherapy for ovarian, lung, and colorectal cancer patients was only given to in-patients. The low bed-capacity probably reduced the chance of getting chemotherapy on time and is reflected by the comparably higher amount of patients left without therapy (48.3%).

A study from 2007 found rates of 50–60% of cancer therapy discontinuation in children in low-income countries, constituting a major cause of therapeutic failure [38]. Although these statistics relate to childhood cancer, our findings are similar and underline the need for improvement in cancer care.

In this population-based cohort we found a very long waiting time for radiotherapy of 6.9 months for patients eligible and a large portion of patients (23.9%) who never received their planned therapy. Similarly, a hospital cohort-study from Ethiopia mentioned the considerable

amount of cervical cancer patients, who died while waiting for therapy and those patients, who outlasted their waiting time with significantly increased cancer stages. Proportions of advanced FIGO-stages over a time period of 2 months increased from 44.2% to 68.3% [23]. Such stage-migration would probably be even worse in our study with a median waiting time of around 6.9 months, showing a unique result due to lack of data from other African countries. Requirements for radiotherapy are considered much higher in low-income countries due to late stage presentation and thus, more commonly used palliative therapy concepts including radiotherapy [39]. A recent IAEA study showed a median unmet need for radiation in developing countries of 47% [40]. Having only one single Cobalt-60 machine in use for the whole of Ethiopia, waiting time will continue to increase due to the increasing patient load and prolonged radiation-times resulting from the decreasing efficacy of the machine.

Outlook

This study shows the challenges Ethiopia is facing in the fight against cancer by looking more closely at population-based provision of cancer therapy. Despite the deficits, steps have been taken to improve the situation. A new oncology program for nurses was established in 2015, the first oncology residents have completed their 4-year training in 2017 and a new oncology outpatient center opened at the beginning of 2016. A national cancer control program has been approved and cervical cancer screening has started. Moreover, new radiotherapy-machines were ordered. These changes are hopeful and demonstrate the increased cancer awareness of politicians and policy makers. At the moment, however, it is impossible to serve the demand for cancer care in Ethiopia.

Limitations

This study has some limitations. Despite our population-based approach, files could only be retrieved for about half of the patients selected from the registry. We assume those without files retrieved have likely not received any therapy. Information about patients with early deaths might also be underrepresented. Therefore, our cohort tends to represent the best treated patients in the country and population-based access to cancer therapy is probably lower. Furthermore, being a retrospective study, some information might have been misinterpreted due to incomprehensible documentation. We assume this is at random. We grouped patients in need of a specific therapy according to general guidelines as the basis to analyze the completeness of therapy. We were unable to account for individualized therapy approaches in stage four patients, any non-standard therapy could have falsely been classified as not complete. Personal therapy recommendations by the physician or individual reasons of the patient not to plan access to such guidelines could not be taken into account due to inconsistent documentation. Therefore, patients classified as „not received", despite guideline recommendation may well have had their own reasons not to receive therapy. Besides, therapy might have been delayed by patients themselves due to individual reasons and have lead to longer waiting times.

Conclusion

In this study, we present completeness of cancer therapy and waiting time as documented from 588 out of 1149 patients of the only population-based cancer registry in Ethiopia. Our findings that only half of those patients received adequate chemotherapy and one fourth received adequate radiation underscores the need for system-wide measures to improve delivery of cancer care. We were unable to obtain detailed reasons for non-adherence to therapy-whether this was a problem on the health care provider's, on patients'or on the logistics side. The known lack of staff, chemotherapy and radiotherapy capacities strongly points towards a

critical shortage of health care provision rather than patient decisions against therapy. We also saw that waiting time for chemotherapy was relatively short (2.1 months) compared to waiting time of 6.9 months for radiotherapy, which clearly shows the need for additional radiotherapy facilities. Once therapy was started, the drop-out rate for both therapies was relatively low (definite 9.9% for chemo- and 2.1% for radiotherapy) which points towards good patient adherence and service delivery. The results of this population-based study show the tremendous challenges Ethiopia is facing in the fight against cancer with need for expansion of existing structures to improve access to timely, cost-effective and high-quality care [41].

Supporting information

S1 Table. Addis ababa cancer registry data.
(XLSX)

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Global Health and Cancer

Cervical Cancer in Sub-Saharan Africa: A Multinational Population-Based Cohort Study of Care and Guideline Adherence

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Cervical cancer • Sub-Saharan Africa • Population-based • Access to care • Radiotherapy • Survival

Abstract

Background. Cervical cancer (CC) is the most common female cancer in many countries of sub-Saharan Africa (SSA). We assessed treatment guideline adherence and its association with overall survival (OS).

Methods. Our observational study covered nine population-based cancer registries in eight countries: Benin, Ethiopia, Ivory Coast, Kenya, Mali, Mozambique, Uganda, and Zimbabwe. Random samples of 44–125 patients diagnosed from 2010 to 2016 were selected in each. Cancer-directed therapy (CDT) was evaluated for degree of adherence to National Comprehensive Cancer Network (U.S.) Guidelines.

Results. Of 632 patients, 15.8% received CDT with curative potential: 5.2% guideline-adherent, 2.4% with minor deviations, and 8.2% with major deviations. CDT was not documented or was without curative potential in 22%; 15.7% were diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IV disease. Adherence was not assessed in 46.9% (no stage or follow-up documented, 11.9%, or records not traced, 35.1%). The largest share of guideline-adherent CDT was observed in Nairobi (49%) and the smallest in Maputo (4%). In patients with FIGO stage I–III disease (n = 190), minor and major guideline deviations were associated with impaired OS (hazard rate ratio [HRR], 1.73; 95% confidence interval [CI], 0.36–8.37; HRR, 1.97; CI, 0.59–6.56, respectively). CDT without curative potential (HRR, 3.88; CI, 1.19–12.71) and no CDT (HRR, 9.43; CI, 3.03–29.33) showed substantially worse survival.

Conclusion. We found that only one in six patients with cervical cancer in SSA received CDT with curative potential. At least one-fifth and possibly up to two-thirds of women never accessed CDT, despite curable disease, resulting in impaired OS. Investments into more radiotherapy, chemotherapy, and surgical training could change the fatal outcomes of many patients. ***The Oncologist*** 2021;26:e807–e816

Implications for Practice: Despite evidence-based interventions including guideline-adherent treatment for cervical cancer (CC), there is huge disparity in survival across the globe. This comprehensive multinational population-based registry study

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aimed to assess the status quo of presentation, treatment guideline adherence, and survival in eight countries. Patients across sub-Saharan Africa present in late stages, and treatment guideline adherence is remarkably low. Both factors were associated with unfavorable survival. This report warns about the inability of most women with cervical cancer in sub-Saharan Africa to access timely and high-quality diagnostic and treatment services, serving as guidance to institutions and policy makers. With regard to clinical practice, there might be cancer-directed treatment options that, although not fully guideline adherent, have relevant survival benefit. Others should perhaps not be chosen even under resource-constrained circumstances.

Introduction

Cervical cancer (CC) shows large differences in outcome globally depending on stage at presentation to the health system and access to high-quality care. Both may vary depending on individual patient factors and local or country-specific availability of diagnostic and treatment services. Assessing of treatment guideline adherence at the patient level and linking this to outcome is an established approach [1, 2]. This is a multinational, population-based study of the pattern and degree of adherence to guidelines of care, and its association with outcome, in patients with CC in sub-Saharan Africa (SSA).

The burden of CC is currently decreasing in high-income countries. For example, age-standardized annual incidence of CC in the U.S. fell to 7.4 in 100,000 in 2010–2014 from more than 40 in 100,000 in 1947–1948 largely because of wide dissemination of screening during this period [3]. In contrast, in SSA—without comprehensive screening—age-standardized incidence rates range from 26.8 in Central Africa to 43.1 in 100,000 in Southern Africa, with Zimbabwe even reporting 62.3 in 100,000 in 2018. Of the estimated 570,000 CC diagnoses and 311,000 cervical cancer deaths in the world in 2018, 112,000 (20%) of new diagnoses and 76,000 (24%) of the deaths occur in SSA [4], despite SSA accounting for only 9.4% of women older than 20 years worldwide [5].

Population-based data on stage at diagnosis are limited in SSA, and those that are available report a substantial proportion of cervical cancer cases diagnosed at late stages. For example, 30% of patients in Uganda presented with International Federation of Gynecology and Obstetrics (FIGO) stage III–IV disease, and 58% of patients in Zimbabwe presented with regional and metastatic disease [6, 7]. With a higher proportion of staged patients, but more selective by nature, recent hospital cohorts yield comparable stage patterns, for example, 81% with stage IIb–IV in a center in Addis Ababa, Ethiopia [8].

Similarly, population-based survival data for CC are limited, but a recently published large survey reports age-standardized relative survival (ASRS) of 69.8%, 44.5%, and 33.1% at 1, 3, and 5 years [9]. Additionally, there are premillennium cohorts that report 49% 5-year ASRS in Uganda and 45% 3-year ASRS in Zimbabwe [6, 7].

The situation of CC care in SSA from a health care infrastructure point of view can be gauged first from the gaps between calculated need and actual availability of radiotherapy services [10] and, secondly, from Global Surgery 2030's estimate that 93% of SSA's population does not have access to safe, timely, and affordable surgery [11]. In addition, although access to chemotherapy is increasing, it is still limited, and its safe administration is a major concern where there is a shortage of oncology personnel [12].

The consequences of these shortfalls in SSA health care systems have so far rarely been examined at an individual level. No previous study has described the pattern of CC care and guideline adherence using a population-based approach, nor has there been a longitudinal examination of the degree to which guideline adherence is linked to survival of patients with CC in SSA. This led to our main research questions: Firstly, what is the quality of CC therapy in SSA in terms of degree of guideline adherence? Secondly, to what extent is overall survival associated with therapy guideline adherence when adjusted for patient characteristics and stage?

With its multinational collection of registry data and multimodal evaluation of degree of therapy guideline adherence, the present study adds population-based evidence on status of CC care and outcomes in a SSA setting.

Materials and Methods

Study Design

This is a multinational retrospective population-based study, drawing patients from nine population-based cancer registries: Abidjan (Ivory Coast), Addis Ababa (Ethiopia), Bamako (Mali), Bulawayo (Zimbabwe), Cotonou (Benin), Eldoret (Kenya), Kampala (Uganda), Maputo (Mozambique), and Nairobi (Kenya). These registries cover populations between 800,000 (Cotonou) and four million (Abidjan) inhabitants. All are members of the African Cancer Registry Network (AFCRN), which since 2013 has coordinated sub-Saharan population-based cancer registries as the International Agency for Research on Cancer's regional hub [13].

Sources of Data and Study Population

After excluding cases registered based on a death certificate only, random samples of patients diagnosed with invasive cancers of the cervix (International Classification of Diseases-10 C53.x) between January 1, 2010, and June 30, 2016, were drawn within the sampling frame of the database of the African Cancer Registry Network. In Addis Ababa, we included all cases diagnosed from January to March 2012 and 2014. A sample size of 700 produces a two-sided 95% confidence interval with a width equal to 0.075 when the sample proportion of patients with adequate care is 0.500. We drew a simple random sample of 45 to 125 patients per registry (mean n = 75) to amount to 700 patients. For logistic reasons, it was impossible to include all patients diagnosed in that period. Follow-up was open for 7 years until December 31, 2017 (Fig. 1).

Data collection was integrated into registration work, based on the AFCRN Standard Procedure Manual Version 2 [14]. The databases of the participating registries include basic demographic and tumor characteristics (including basic

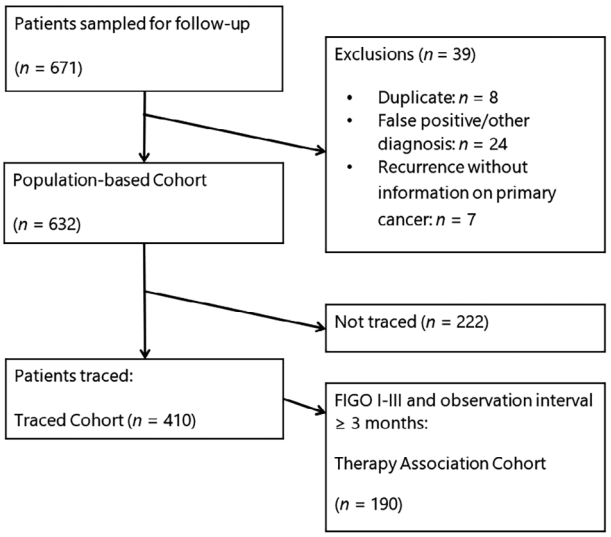

Figure 1. Trial flow diagram. Patients with hospital files found or successful telephone contact were considered to be traced. Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

staging) and, infrequently, basic initial treatment data. Clinical records of registered cases were traced via the source(s) recorded in the registry, information on date of diagnosis and stage was verified or updated, and any duplicates were excluded (Fig. 1). The registry records were updated with information on diagnostic procedures, treatment received, and patients' vital status. However, if this information could not be found in clinical records, we attempted to contact the patient or their relatives through all phone numbers available in the records and hospital information systems to ascertain treatment details and survival status. This also enabled us to inquire about within-country and international referral undocumented in the records. Cases for which a health record or additional information was found after this active follow-up are subsequently referred to as "traced cases" and "traced cohort."

Stage at diagnosis was obtained from physicians' clinical assessments in the records in line with FIGO's 2009 classification [15]; T1–T3 with radiologically or pathologically positive pelvic nodes were grouped as FIGO stage III. In some cases, clinical FIGO stage was amended by additional information from imaging or pathology findings in line with the abovementioned AFCRN Manual. Performance status at diagnosis as Eastern Cooperative Oncology Group (ECOG) score was collected. Four detailed aspects of cancer-directed therapy (CDT) were recorded: surgery, external beam radiation therapy (EBRT), brachytherapy, and chemotherapy. When details such as hysterectomy or radiotherapy dose were not further specified but the record reported "complete," we assumed the treatment was performed with adherence to guidelines as a necessary simplification.

Therapy Evaluation

U.S. National Comprehensive Cancer Network (NCCN) CC Guidelines 1.2010 (actually prepared for the high-income setting) reflected the optimum standard of CC care at the beginning of our study period [16]. These were in widespread use in low- and middle-income countries and parts of SSA and were therefore chosen as a point of reference [17, 18]. Physicians also used locally adapted guidelines, other guidelines, or adjusted treatment according to specific patient characteristics and resource limitations. Because of the retrospective nature of the study using real-world data, these factors were not captured in our analytical database. Still, we aimed to use NCCN Guidelines as standard to give an overall picture on access to care rather than a posteriori judging the individual treatment decisions. We compiled a scheme for evaluating degree of adherence (Table 1). Guideline adherence was assessed for cases known to be FIGO stage I–III. Each stage-dependent category includes key procedures and modalities required to reach a certain degree of adherence. Note that not all possible treatment variations were depicted, and possible overtreatment was not the focus of the study. "Guideline-adherent" was the minimum sufficient therapy recommended. Courses of chemotherapy alone, EBRT <45 Gy, and surgical intervention without removal of the tumor were defined as "CDT without curative potential."

Outcome

Outcome, in terms of date and vital status (alive/dead) at the last known contact, as recorded by the cancer registries, was verified and/or updated from the clinical records. When no information could be found, contact by telephone with the patient or next of kin was attempted. The precise cause of death, as certified by a medical practitioner, could rarely be determined.

Statistical Methods

Overall survival (OS) was estimated using the Kaplan-Meier method, and differences according to prognostic factors were assessed with the log rank test. ASRS was calculated for the traced cohort. Relative survival was determined using SAS macro "periodh" [19]. Because of the small number of patients per registry per year and because differences in baseline mortality of the age groups studied between the countries were small (see supplemental online Table 2) [20], only a single life table was created: World Health Organization life tables from the eight countries for the year 2013 as the median year of diagnosis of all patients were retrieved and the average calculated [20]. For age standardization the direct method and International Cancer Survival Standard 2 with its "broad age groups" were employed [21]. We assume that the small sample of cases (632) is representative of cervix cancer cases in sub-Saharan Africa and that the missing cases (35% of patients who cannot be traced; 2% of patients whose files that miss staging information) were missing at random. Extrapolation of therapy evaluation results for SSA was done by using simple multiplication with rounding to 1,000 and assuming representativeness and missing information at random.

To assess the association between treatment guideline adherence and survival, Cox multiple regression was employed for the therapy association cohort (follow-up $\geq$3 months, FIGO stage $\leq$III). The inclusion criteria were chosen to reduce survivorship bias. The assumption of

Table 1. Therapy evaluation scheme for patients with known FIGO stage

Therapy; FIGO stage	Guideline adherent (FIGO stage I–III applicable only)	Minor deviation (FIGO stage I–III applicable only)	Major deviation (FIGO stage I–III applicable only)	CDT without curative potential (FIGO stage I–III applicable only)	No CDT detected, FU <3 months (FIGO stage I–III applicable only)	No CDT detected, FU ≥3 months (FIGO stage I–III applicable only)
Curative primary surgery						
IA1	Excision with free margins, e.g., through conization, simple hysterectomy	—	Any cancer-directed surgery with possible tumor destruction, e.g., laser vaporization or cryotherapy	—	No CDT identified, but patient dead/ lost to FU <3 months after diagnosis	No CDT identified in patients with FU ≥3 months
IA2–IIA	(IA2: Modified) Radical hysterectomy + pelvic LAE	(IA2: Modified) Radical hysterectomy	Any less radical procedure for removal of tumor, e.g., simple hysterectomy	Any surgery with remaining parts of cervix/ primary tumor	No CDT identified, but patient dead/ lost to FU <3 months after diagnosis	No CDT identified in patients with FU ≥3 months
IIB	—	Radical hysterectomy + pelvic LAE	Radical hysterectomy	Any less radical surgery than radical hysterectomy	No CDT identified, but patient dead/ lost to FU <3 months after diagnosis	No CDT identified in patients with FU ≥3 months
Curative primary radiotherapy						
IB–III	EBRT ≥45 Gy + concurrent chemotherapy ≥2 cycles + brachytherapy ≥16.6 Gy	EBRT ≥45 Gy + brachytherapy ≥16.6 Gy	EBRT ≥45 Gy (with or without chemotherapy	EBRT <45 Gy or missing	No CDT identified, but patient dead/ lost to FU <3 months after diagnosis	No CDT identified in patients with FU ≥3 months
T1–3 N1	EBRT ≥45 Gy + concurrent chemotherapy ≥2 cycles + brachytherapy ≥16.6 Gy if primary is not resected	EBRT ≥45 Gy + brachytherapy ≥16.6 if primary is not resected	EBRT ≥45 Gy (with or without chemotherapy)	EBRT <45 Gy or missing	No CDT identified, but patient dead/ lost to FU <3 months after diagnosis	No CDT identified in patients with FU ≥3 months
Obligatory palliative care: IVA–IVB	Individual approaches with or without CDT, labeled "FIGO stage IV, any approach"					

Therapy was considered for evaluation if documented within 2 years and not indicated for relapse. References and considerations on which this scheme is based apart from National Comprehensive Cancer Network Guidelines version 1.2010 can be found in supplemental online Table 1.
Abbreviations: CDT, cancer-directed therapy; EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; FU, follow-up, observation after date of incidence; LAE, lymphadenectomy; N1, radiologically or pathologically involved pelvic lymph nodes.

proportionality of hazards was checked graphically and found to be satisfactory.

Ethics

The study protocol was approved by the AFCRN review committee (02.03.2016) and Halle University Review Board (votum no. 2019-009). The study group used anonymized secondary data, which were collected under existing regulations and national laws in the respective registries. Funding sources had no role in study design, collection, analysis, or interpretation of the data.

Results

The median age at diagnosis in our population-based cohort was 50 years. The most common stage was FIGO III, and the most common histology was squamous cell carcinoma (Table 2).

For the population-based cohort (n = 632) in general, we found that about one-eighth of patients had received some form of external beam radiotherapy (EBRT) and one-eighth some form of surgery. Information additional to that recorded by the cancer registries could not be found for 35% of the patients. Of the patients we could trace

(*n* = 410), more than half (or 31% of the total cases) lacked essential information for therapy evaluation. Guideline adherence of care varied according to FIGO stage group (supplemental online Table 3).

Quality and delay of radiotherapy were assessed. Only one-fifth of the traced cohort (*n* = 410) received primary EBRT. In detail, there were 73 nonsurgical patients, and of these 60 (82%) were staged FIGO I–III in need of curative EBRT with concurrent chemotherapy and subsequent brachytherapy [16]; of these latter 60 patients in need, 8 (13%) were documented as certainly incomplete. Furthermore, only 8 (13%) of 60 patients had brachytherapy as part of their treatment, and only 22 (37%) of 60 patients received concurrent chemotherapy. A median delay of 14 weeks (range, 1–73 weeks) between diagnosis and the start of EBRT was noted in 45 patients whose files had exact EBRT dates.

Radiation was also incomplete for 10 patients with node-positive disease who had received operations. Only three of them had documented EBRT after surgery, whereas four of the remaining seven patients with node-positive disease were observed for ≥12 months without EBRT.

Chemotherapy as the only CDT was seen in 66 (16%) of patients in the traced cohort, of whom there were 42 (64%) patients with FIGO stage I–III. Eighteen (43%) of these 42 patients were observed for more than 12 months without further CDT being documented.

Statements on guideline adherence and quality of care were possible for two-thirds of traced patients. Evaluation was impossible for one-third of traced patients because of lack of information on stage, early death, and observation less than 3 months. When we evaluated the degree of guideline adherence among the whole population-based cohort, the proportion of patients with known optimal guideline-adherent therapy came down to a total of only 5%; an additional 11% received therapy with curative potential showing minor or major deviations (Fig. 2). The proportions of guideline-adherent therapy were higher among patients with early stages compared with late-stage presentation (see supplemental online Table 3 and supplemental online Fig. 1). A total of 19% of patients certainly received therapy without curative potential or no therapy at all. In the worst-case scenario, that is, no further CDTs in the untraceable patients, this would mean that only 16% received any CDT with curative potential, whereas 67% of patients were receiving CDT without curative potential or no therapy at all. Additionally, 17% of patients were known FIGO stage IV in need of palliative care (Fig. 2).

We found large disparities in care within the populations of the different countries. Populations from centers with radiotherapy available (Addis Ababa, Kampala, and Nairobi) had higher proportions of patients with guideline-adherent therapy or minor and major deviations compared with those centers without radiotherapy facilities (Fig. 3).

Data come from eight countries only, but to highlight the possible broader implications of our findings, we extrapolated the findings of our cohort to all 112,000 estimated newly diagnosed cervical cancer cases each year in SSA [4]. This translated to 9,000 (8%) patients with FIGO stage I–III who received guideline-adherent care, 4,000 (4%) with FIGO stage I–III who received minor deviations and 15,000 (13%) major deviations, 19,000 (17%) with FIGO stage I–III who received CDT without curative potential, 19,000 (17%) more patients with FIGO stage I–III who did not receive any CDT though observed beyond 3 months, 18,000 (16%) patients with FIGO stage I–III who died or got lost to follow-up within 3 months of diagnosis and had no CDT documented, and

Table 2. Patient characteristics of the population-based cohort (*n* = 632)

Characteristics	*n* (%)
Age group (median: 50 years; IQR: 40–58 years; range 16–99 years)	
<40 years	143 (23)
40–59 years	335 (53)
≥60 years	154 (24)
Registry	
Abidjan, Ivory Coast	67 (11)
Addis Ababa, Ethiopia	92 (15)
Bamako, Mali	59 (9)
Bulawayo, Zimbabwe	55 (9)
Cotonou, Benin	37 (6)
Eldoret, Kenya	82 (13)
Kampala, Uganda	60 (9)
Maputo, Mozambique	122 (19)
Nairobi County, Kenya	59 (9)
HIV status	
Negative	78 (12)
Positive	82 (13)
Unknown	250 (40)
Not traced	222 (35)
ECOG performance	
ECOG 0–1	88 (14)
ECOG 2	61 (10)
ECOG 3–4	25 (4)
Unknown	236 (37)
Not traced	222 (35)
FIGO stage	
I	49 (8)
II	91 (14)
III (incl. T1–T3, pelvic N1)	123 (19)
IV	99 (16)
Unknown	48 (8)
Not traced	222 (35)
Histology	
Squamous cell carcinoma	443 (70)
Adenocarcinoma	40 (6)
Other	4 (1)
Carcinoma	41 (6)
Neoplasm, malignant	104 (16)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range.

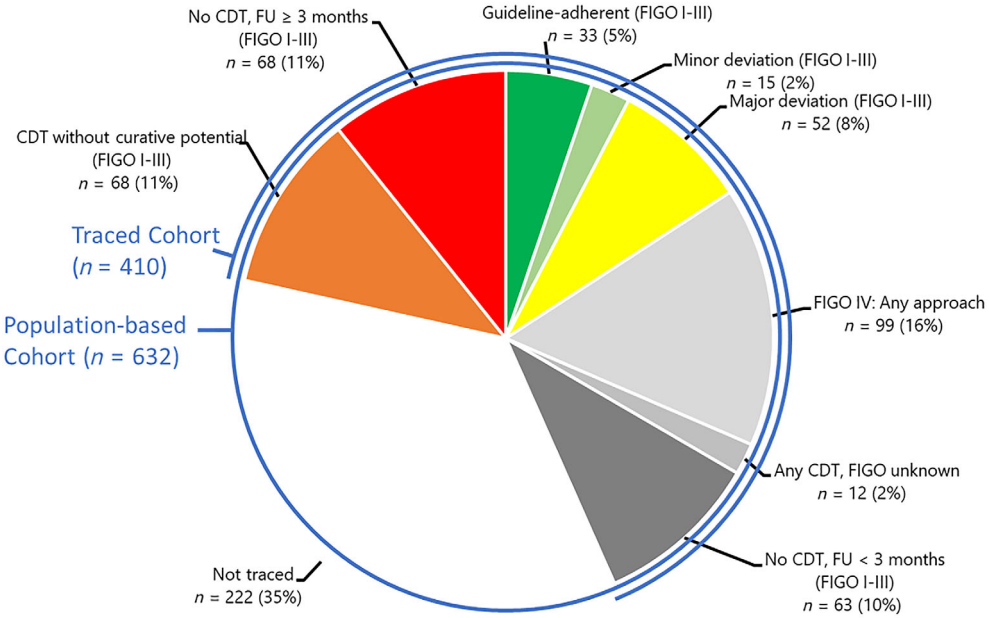

Figure 2. Therapy evaluation in the population-based cohort (*n* = 632). Evaluations refer to the therapy evaluation scheme in Table 1. Colors depict the degree of adherence: green indicates optimal, light green minor deviation, yellow major deviation, orange CDT without curative potential, and red no CDT. Light gray indicates patients with FIGO stage IV, middle and darker gray indicates missing stage or observation time, and no color indicates untraced patients. Patients with hospital files found or successful telephone contact were considered to be traced.
Abbreviations: CDT, cancer-directed therapy; FIGO, International Federation of Gynecology and Obstetrics; FU, follow-up (time of observation since diagnosis).

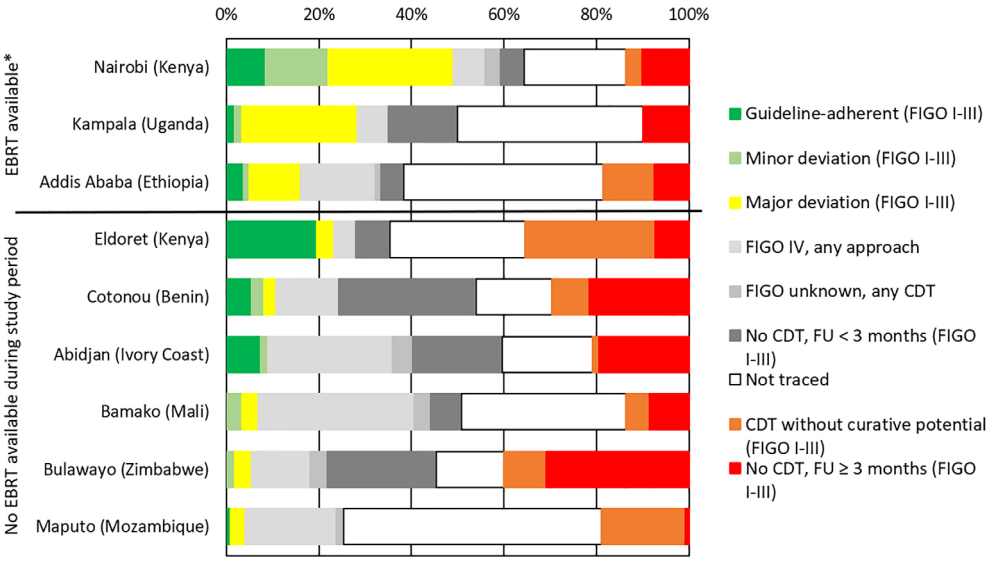

Figure 3. Therapy evaluation in the population-based cohort (*n* = 632) stratified by registry. Evaluations refer to the therapy evaluation scheme in Table 1. Colors depict the degree of adherence: green indicates optimal, light green minor deviation, yellow major deviation, orange CDT without curative potential, and red no CDT. Light gray indicates patients with FIGO stage IV, middle and darker gray indicates missing stage or observation time, and white indicates the proportion of untraced patients. *, Principal EBRT availability at the study site did not exclude overstrain or temporary breakdown of machines. EBRT in Bulawayo was nonfunctional during the whole study period.
Abbreviations: CDT, cancer-directed therapy; EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; FU, follow-up (time of observation since diagnosis).

28,000 (25%) patients who were diagnosed with FIGO stage IV and, hopefully, were subject to individualized care. Patients in the inconclusive categories "Not traced" (*n* = 222) and "Any CDT, FIGO unknown" (*n* = 12) were omitted at this point.

OS in the traced cohort (*n* = 410) at 1, 2, and 3 years was 74% (95% confidence interval [CI], 69.3%–78.7%), 51.3% (95% CI, 45%–57.6%), and 41.3% (95% CI, 34.6%–48%), respectively (Fig. 4). A total of 22 patients died within the first month (median at 7 days) after formal diagnosis.

One-, 3-, and 5-year ASRSs were 75.6% (95% CI, 70.9%–80.3%), 42.4% (95% CI, 35.5%–49.7%), and 28.7% (95% CI, 19.9%–37.5%). OS differed between FIGO stages I and II versus stages III and IV ($p < .001$). Three-year OS was similar for women with FIGO stage I and II cancer (60.8% and 58.2%) but considerably lower for women with FIGO stage III and IV cancer (27.8% and 17.8%) (supplemental online Fig. 2).

Multiple Cox regression analysis was done with adjustment for FIGO stage, age group, HIV status, and ECOG performance status among patients with known stage and more than 3 months' observation time. Lack of CDT was the variable most strongly associated with negative effect on survival. CDT without curative potential (hazard rate ratio [HRR], 3.88; 95% CI, 1.19–12.71) and no CDT (HRR, 9.43; 95% CI, 3.03–29.33) were associated with worse survival. Minor (HRR, 1.73; 95% CI, 0.37–7.37) and major deviations (HRR, 1.97; 95% CI, 0.59–6.56) were associated with somewhat worse survival. FIGO stage III (HRR, 2.21; 95% CI, 1.01–4.48) and HIV positivity (HRR, 2.00; 95% CI, 1.01–3.96) status were also associated with worse survival (Fig. 5).

To facilitate quantitative comparison with a 2005–2011 Australian cohort [22], we additionally analyzed a subcohort including only patients with FIGO stage I and II ($n = 111$). In this subcohort, adherence to guidelines was associated with a substantially better survival (HRR, 0.30; CI, 0.11–0.86).

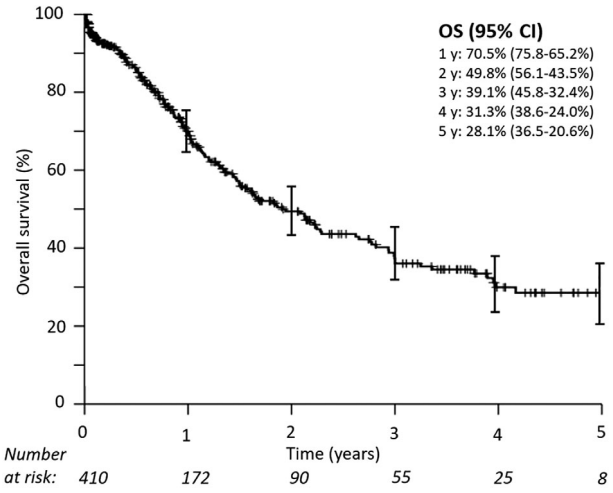

Figure 4. Overall survival in the traced cohort ($n = 410$). Median overall survival was 23 months. Patients with hospital files found or successful telephone contact were considered to be traced.
Abbreviations: CI, confidence interval; OS, overall survival.

Discussion

The most alarming finding in our population-based, cross-sectional assessment of NCCN Guidelines–recommended receipt of therapy in eight SSA countries was that for two-thirds of patients with CC, no documented CDT could be found despite thorough investigations, and in the worst-case scenario, these patients did not receive any CDT at all. Additionally, of the 37% patients with valid treatment evaluation, only half received CDT with curative potential. By country, the proportion of patients receiving CDT with curative potential varied from 4% in Maputo (Mozambique) to 49% in Nairobi (Kenya). But also, within countries we saw huge inequality. Our study was performed mainly in capital cities (exceptions: Eldoret and Bulawayo, both still major centers). All have tertiary referral oncology centers, which, however, were only partly equipped with radiotherapy facilities, and patients within population-based registry areas lived close to

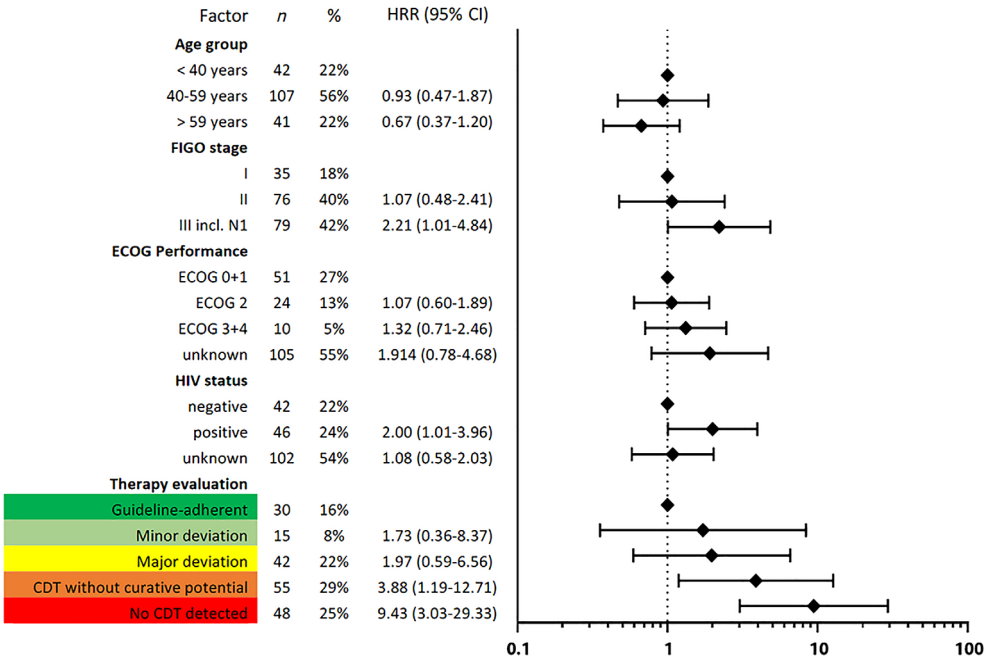

Figure 5. Results of multiple Cox regression for risk of early death in the therapy association cohort ($n = 190$) are shown: through inclusion criteria (FIGO stages I–III and follow-up ≥3 months), bias was reduced. Therapy evaluation refers to Table 1.
Abbreviations: CDT, cancer-directed therapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRR, hazard rate ratio.

those centers. According to international recommendations, all centers had far too few radiotherapy facilities [23]. In this respect, we found that cancer centers in registry areas with EBRT available managed to provide CDT with curative potential to only 15%–49% of patients (Addis Ababa, Nairobi, and Kampala), whereas only 10% of patients in countries without radiotherapy facilities received CDT with curative potential—except Eldoret (Kenya) with 23%, where we know that a screening program is in place [24]. In general, economic, epidemiologic, and radiotherapy indicators confirm differences between the countries in our scope but also the backlog relative to Australia and the U.S., which we used for comparisons elsewhere in this report (supplemental online Table 4).

Excluding subjects with missing information, our estimated findings imply that only 28,000 of 112,000 annual patients with CC in SSA received CDT with curative potential [4]; 38,000 up to 56,000 received CDT without curative potential or no CDT. Approximately 28,000 patients presented in FIGO stage IV needing palliative care. These projections are optimistic because they assume that results in large city situations are generalizable to the whole population, including rural settings where access to therapy is likely to be worse.

In general, care of patients with CC requires specialized multimodal therapy with radiotherapeutic and surgical options. This applies to an even greater extent to patients with FIGO stage ≥II (86.5% of patients with staging information available). Given the patient pathways and observed treatment patterns, we assume that certain factors may have greatly reduced the proportion of patients receiving guideline-adherent care. The identified problems include a lack of specialized facilities and personnel for diagnosis [25], surgery [11], interrupted provision of chemotherapy drugs [12], and both individual poverty and lack of health insurance. The well-known and still widespread lack of EBRT and brachytherapy services has great impact and is also seen in our cohort [10]. Only 13% of patients with known FIGO stages I–III received primary EBRT and brachytherapy. This is comparable to findings from a population-based Ugandan cohort of 261 patients described 20 years ago (1995–1997): only 25% of patients with FIGO stages I–IV received primary EBRT and brachytherapy [6]. In contrast, in the Surveillance, Epidemiology, and End Results (SEER) program areas of the U.S., 59%–83% of patients with FIGO stages IB2–IVA received adequate radiotherapy in 1988–2009 [26]. Similarly, in Australia, treatment for patients with FIGO stages I–IVa was guideline adherent for more than half (54.1%) of the patients in 2005–2011 [22]. Our most important result of 16% strict guideline adherence among 190 patients (in the therapy association cohort; Fig. 5) is by far the lowest rate reported in the literature to this date.

This low adherence was associated with poor outcome. Analysis of survival showed 1-, 3-, and 5-year-ASRSs of 75.6%, 42.4%, and 28.7%. This survival is similar to Ugandan (81.4% and 49%) and Zimbabwean (66% and 44.9%) 1995–1997 population-based 1- and 3-year ASRS estimates, although the reference population for standardization slightly different [6, 7]. In contrast, the U.S. SEER estimate of 67.1% 5-year ASRS for the 2007–2013 period [27], taken as example of CC survival in a high-income country, is much higher. As expected, patients with FIGO stages I and II had considerably better outcome probabilities than those with FIGO stages III and IV. This should encourage education of health care workers to be able to recognize and interpret symptoms of CC and refer patients earlier.

Using the patient group with known FIGO stages I–III and ≥3 months' observation time, we analyzed the effect of known prognostic factors and degree of treatment completeness on outcome. In 2017, NCCN published Harmonized Guidelines specific to low-resource regions such as SSA [28]. These guidelines contain information on standard treatment, but also alternative options when resources are not available. The impact of an implementation of these NCCN Harmonized Guidelines for SSA obviously cannot be assessed in a randomized trial. The relationship between different degrees of therapy adherence and better survival observed in our study supports these guidelines' principles of recommending well-considered, specific deviations from maximum care if needed. Association of therapy with survival followed a dose-response effect, with the HRRs increasing with less guideline adherence. Treatment with minor deviations was associated with 1.7-times increased risk of death, major deviations were associated with a doubled hazard ratio, and "CDT without curative potential" and "no CDT" were associated with detrimental fourfold and ninefold higher hazards of death, respectively, compared with guideline-adherent treatment. As we do not expect extensive short-term improvements in CC care in SSA, we conclude that therapy with selected minor and major deviations (Table 1) such as recommended in the NCCN Harmonized Guidelines for SSA are justifiable options.

Treatment attempts without curative potential should be avoided, such as discontinuation of radiotherapy resulting in underdosing, chemotherapy only, surgery in patients with FIGO stage >IIb, or inappropriate surgery in patients with FIGO stage ≤IIb. We found that such practices were associated with a nearly fourfold risk of early death compared with guideline-adherent practices. It is also possible that they cause considerable morbidity as well as financial burden in patients and family members [29]. Of course, it is even less acceptable to see patients managed without any CDT in a curative situation, with risk of early death increased ninefold.

In patients with fully guideline-adherent treatments, the risk of early death was similar in our study (HRR, 0.30; 95% CI, 0.11–0.86; n = 111) compared with an Australian subcohort with FIGO stage I and II patients (HRR, 0.22; 95% CI, 0.07–0.75; n = 106) in 2005–2011 [22].

General limitations in our study include imprecise staging, poor documentation and record keeping, and early loss to follow-up [6–9, 30]. First, to assess completeness of therapy, we included patients from the population-based registries, among which there is no selection bias in contrast to hospital-based studies. Second, we assume there could have been a survivorship bias, because patients with aggressive disease and early death never had a chance to receive therapy and thus could have contributed to lower survival in the group without therapy. We also anticipated immortal-time bias for those patients receiving treatment. Therapy uptake might not have been at random but also might have been

linked to factors associated with outcome. To reduce inflation of therapy effects, we only included into regression analysis patients with survival of at least 3 months after diagnosis. Consequently, the analysis started 3 months after diagnosis [31]. Third, patients without any information were a large group of 35%. We decided not to make assumptions about therapy received and to present the data as unknown. Findings on stage pattern, number of patients left untreated, 1- and 3-year ASRSs, and proportion of HIV-positive patients were similar to previous studies from Ethiopia, Kenya, and Zimbabwe and reassuring as to the representativeness of our cohort [6–8]. Seeing a total of 22 among 410 patients in the traced cohort who died within the first month (median survival 7 days) shows that late presentation and late formal diagnosis is another reason for very short survival times in our cohort. Upcoming prospective studies from population-based cancer registries may result in more detailed information on therapy and outcome [32].

Conclusion

In this population-based study from eight African countries, up to two-thirds of patients with CC received treatment without curative potential or no therapy at all (worst-case scenario assuming those without documented information were left without therapy). Lack of therapy and advanced stage were associated with very low survival rates, similar to data reported 20 years ago from Uganda and Zimbabwe. Implementation of vaccination, early detection, and screening could reduce the total of 112,000 patients with CC and reduce the estimated 28,000 patients with incurable stage IV disease in the long term. More radiotherapy facilities are urgently needed for patients presenting with curative disease. Also, specialist gynecological surgeons need to be trained to mitigate the tragic outcome of up to 75,000 women presenting with curable disease but not receiving guideline-adherent or any treatment at all, who are thus left to suffer and die. Progress in surgical techniques managing even advanced and nodal-positive disease without radiotherapy could be of high importance for SSA [33].

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Disclosures

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bjh research paper

Clinical presentation and diagnosis of adult patients with non-Hodgkin lymphoma in Sub-Saharan Africa

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Summary

Non-Hodgkin lymphoma (NHL) is the sixth most common cancer in Sub-Saharan Africa (SSA). Comprehensive diagnostics of NHL are essential for effective treatment. Our objective was to assess the frequency of NHL subtypes, disease stage and further diagnostic aspects. Eleven population-based cancer registries in 10 countries participated in our observational study. A random sample of 516 patients was included. Histological confirmation of NHL was available for 76.2% and cytological confirmation for another 17.3%. NHL subclassification was determined in 42.1%. Of these, diffuse large B cell lymphoma, chronic lymphocytic leukaemia and Burkitt lymphoma were the most common subtypes identified (48.8%, 18.4% and 6.0%, respectively). We traced 293 patients, for whom recorded data were amended using clinical records. For these, information on stage, human immunodeficiency virus (HIV) status and Eastern Cooperative Oncology Group Performance Status (ECOG PS) was available for 60.8%, 52.6% and 45.1%, respectively. Stage at diagnosis was advanced for 130 of 178 (73.0%) patients, HIV status was positive for 97 of 154 (63.0%) and ECOG PS was ≥2 for 81 of 132 (61.4%). Knowledge about NHL subclassification and baseline clinical characteristics is crucial for guideline-recommended treatment. Hence, regionally adapted investments in pathological capacity, as well as standardised clinical diagnostics, will significantly improve the therapeutic precision for NHL in SSA.

Keywords: non-Hodgkin lymphoma, Sub-Saharan Africa, regional distribution, diagnostics, human immunodeficiency virus, public health.

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Introduction

Non-Hodgkin lymphoma (NHL) is the sixth most common type of malignant neoplasia in Sub-Saharan Africa (SSA), with incidence continuously rising and burden expected to double by 2040 (Parkin *et al.*, 2010; Chokunonga *et al.*, 2013; Bray *et al.*, 2018). NHL is a heterogeneous disease, with >80 subtypes identified (Swerdlow *et al.*, 2016). In SSA, infectious agents are important causes of lymphoma. A recent study reported that ~19.7% of NHL cases in SSA are attributable to infectious agents, with 12.7% of the cases related to human immunodeficiency virus (HIV) alone (Parkin *et al.*, 2019).

Non-Hodgkin lymphoma is aetiologically associated with Epstein–Barr virus (EBV) (Vockerodt *et al.*, 2015), human gammaherpesvirus 8 (Cesarman *et al.*, 1995), *helicobacter pylori* (Zucca *et al.*, 2014), human T-lymphotrophic virus 1 (Cook *et al.*, 2017), and malaria (Thorley-Lawson *et al.*, 2016), and epidemiologically associated with HIV (Grulich *et al.*, 2007; Shiels & Engels, 2012; Carbone *et al.*, 2014; Schonfeld *et al.*, 2016), even when controlled by antiretrovirals (Cesarman, 2013), and hepatitis C virus (Morton *et al.*, 2014; Miranda-Filho *et al.*, 2019). Other environmental, demographic, ethnic and lifestyle factors are likely to play an important role as well (Morton *et al.*, 2014). Identification of NHL subtype is crucial for specific therapy (Naresh *et al.*, 2011; Gopal *et al.*, 2012). In SSA, resources for diagnostic services and cancer care are limited, resulting in a high frequency of unclassified lymphoma and in poor clinical outcome (Gopal *et al.*, 2012; Mwamba *et al.*, 2012; Gopal *et al.*, 2016; Perry *et al.*, 2016b; Milligan *et al.*, 2018). The National Comprehensive Cancer Network (NCCN) developed resource-stratified guidelines on B cell lymphoma (Zelenetz *et al.*, 2019).

To date, data on quality of diagnostics have been published on hospital series only (e.g. Bateganya *et al.*, 2011; Naresh *et al.*, 2011; Wiggill *et al.*, 2011; Gopal *et al.*, 2016; Milligan *et al.*, 2018; Painschab *et al.*, 2019). The aim of the present study was to assess NHL subtype distribution and diagnostic services in a population-based cohort by collaborating with the African Cancer Registry Network (AFCRN). Data from registries in 10 countries were accessed for a retrospective analysis. Hence, the present study will help to provide a more complete picture of lymphoma diagnostics in SSA and contribute to improved diagnostic accuracy and patient management.

Patients and methods

Eleven population-based cancer registries (PBCRs) in 10 countries were selected as study centres, covering a population of ~21.5 million (Fig 1) (Parkin & Liu, 2019). These registries co-operate with oncological facilities, including hospitals and medical practices, in their respective registry areas from both the public and the private sector, and register all patients diagnosed with cancer in databases.

We included patients with NHL aged 15–99 years with International Classification of Diseases (ICD)-10 codes C82-C86 and C96 (April *et al.*, 2013) (Table S1) diagnosed between 2012 and 2013, extending the time period for some

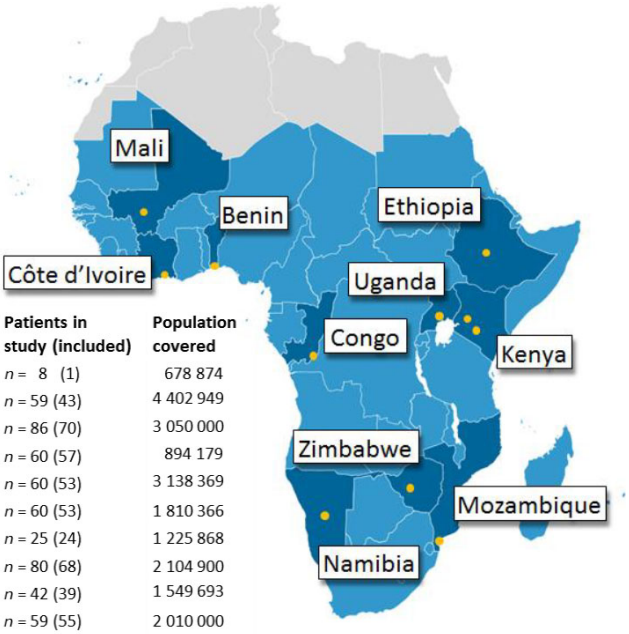
registries due to lack of patients. In total, 1068 patients were available in the registry databases. We assessed prevalence of adequate care from medical records among a random sample that could be assessed within feasible time and efforts in the given setting. We intended to draw conclusions for an SSA cohort, but not for individual registries. Therefore, no power was calculated for individual registries. A minimal sample size of 404 patients produces a two-sided 95% confidence interval with a width equal to 0.1 when the sample proportion of patients with adequate care is 0.500, which is the most conservative assumption. We assumed a drop-out rate of 33% and therefore aimed for 600 patients as our random sample. Thus, of 1068 patients available in registries, 599 patients (56.1%) were selected at random. In Brazzaville, Cotonou and Mozambique, all patients registered were included due to limited number of registered patients (Table I and Fig 2).

The AFCRN registry staff continuously retrieves information from hospital records and pathology reports (Am Finesse *et al.*, 2019). Data on sex and age, diagnosis and diagnostic modality are collected and coded according to current International Classification of Diseases for Oncology (ICD-O) standards (April *et al.*, 2013). To update the PBCR routine data, clinical records were re-evaluated. We considered registry data to be correct, unless the medical record gave differing information. Morphology was assessed from pathology reports, and, in the absence of definitive pathological diagnoses, those noted in clinical records were used.

A total of 41 diagnoses were reported according to Working Formulation classification (Rosenberg, 1982). For summary purposes, 11 diagnoses of '(diffuse) small cell NHL' were converted to 'low-grade NHL, unknown cellular lineage, not otherwise specified (NOS)' (ICD-O code 9591); and 23 diagnoses of '(diffuse) large cell NHL' were converted to 'high-grade NHL, unknown cellular lineage, NOS' (ICD-O code 9591). The remaining seven Working Formulation diagnoses were defined as NHL, NOS (unclassified NHL, ICD-O code 9591). Eight other patients pathologically diagnosed as low-grade NHL (three) and high-grade NHL (five) without any further classification were assigned to ICD-O code 9591, low-grade and high-grade, respectively. The diagnostic modality provided by registries, that is, histology, cytology, or clinical diagnosis without any specimen analysis, was amended if additional information on fine needle aspiration cytology (FNAC) or histological confirmation was found.

Furthermore, we traced data not available in PBCR databases: B symptoms, Eastern Cooperative Oncology Group Performance Status (ECOG PS), stage, HIV status and information on imaging. Stage was assessed in line with Lugano and Binet classification (Cheson *et al.*, 2014; Hallek, 2017). When stage had not been assigned in records, it was considered less advanced if no suggestion of disseminated nodal or extranodal involvement was found. When uncertain about primary or secondary extranodal lymphoma in advanced stages, we considered disease to be primary nodal rather than primary extranodal. Patients were considered to have 'traced clinical information' if information beyond the basic PBCR data was obtained from hospital and pathology records: Stage, B symptoms, ECOG PS, HIV status and imaging. For patients not traced, no information beyond the basic PBCR data was available.

For further analysis, patients were allocated to six groups: subclassified high-grade B cell NHL, subclassified low-grade B cell NHL, subclassified T cell NHL, otherwise subclassified



Population-based cancer registry	Patients in study (included)	Population covered
Benin – Cotonou	*n* = 8 (1)	678 874
Côte d'Ivoire – Abidjan	*n* = 59 (43)	4 402 949
Ethiopia – Addis Ababa	*n* = 86 (70)	3 050 000
Kenya – Eldoret	*n* = 60 (57)	894 179
Kenya – Nairobi	*n* = 60 (53)	3 138 369
Mali – Bamako	*n* = 60 (53)	1 810 366
Mozambique – Maputo	*n* = 25 (24)	1 225 868
Namibia – nation-wide	*n* = 80 (68)	2 104 900
Congo – Brazzaville	*n* = 42 (39)	1 549 693
Uganda – Kampala	*n* = 59 (55)	2 010 000
Zimbabwe – Bulawayo	*n* = 60 (53)	653 000

Fig. 1. Map of Sub-Saharan Africa (Wikimedia Commons, 2019). Countries and cities of participating population-based cancer registries are highlighted; together with number of patients in random sample drawn, number of patients included in the study and population covered in each registry area. [Colour figure can be viewed at wileyonlinelibrary.com]

Table I. Population-based cancer registries (PBCR) and study population characteristics.

PBCR (years observed)	Patients registered in PBCR during years observed, *n*	Population-based sample, *n* (% of patients registered in PBCRs during years observed)	Patients excluded, *n* (% of population-based sample)	Total cohort, *n*	Patients traced, *n* (% of total cohort)
Abidjan (2012–2013)	112	59 (52.7)	16 (27.1)	43	30 (69.8)
Addis Ababa (2012 and 2014)	103	86 (83.5)	16 (18.6)	70	33 (47.1)
Bamako (2012–2013)	61	60 (98.4)	7 (11.7)	53	20 (37.8)
Brazzaville (2011–2014)	42	42 (100)	3 (7.1)	39	6 (15.4)
Bulawayo (2012–2013)	198	60 (30.3)	7 (11.7)	53	36 (67.9)
Cotonou (2013–2014)	8	8 (100)	7 (87.5)	1	1 (100)
Eldoret (2012–2013)	68	60 (88.2)	3 (5.0)	57	21 (36.8)
Kampala (2012–2013)	94	59 (62.8)	4 (6.8)	55	40 (72.7)
Maputo (2014–2015)	25	25 (100)	1 (4.0)	24	17 (70.8)
Nairobi (2012–2013)	196	60 (30.6)	7 (11.7)	53	44 (83.0)
Namibia (2012–2013)	161	80 (49.7)	12 (15.0)	68	45 (66.2)
11 PBCRs (2011–2015)	1.068	599 (56.1)	83 (13.9)	516	293 (56.8)

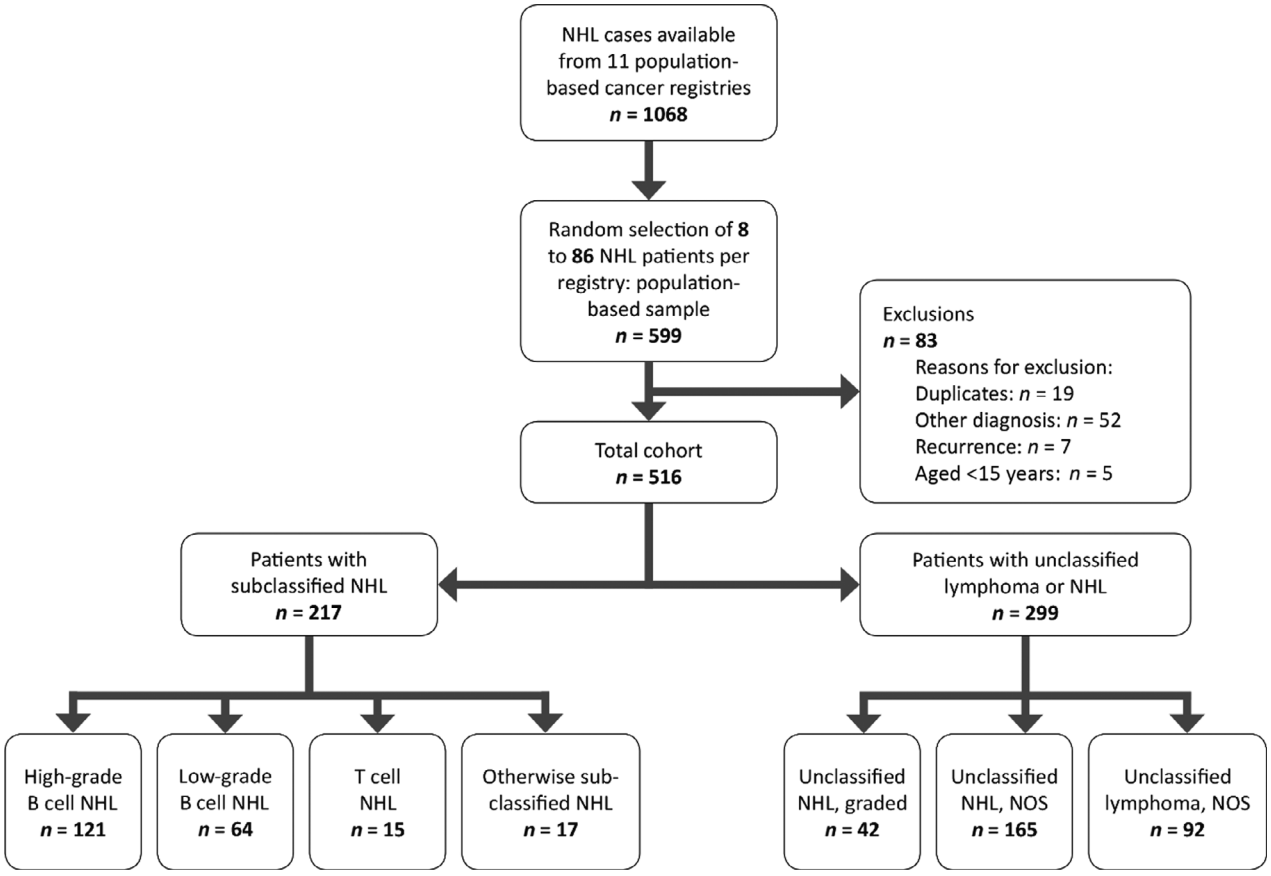


Fig. 2. Flowchart of study population. Stratified by non-Hodgkin lymphoma groups. NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

NHL, unclassified and graded NHL, and unclassified NHL or lymphoma, not graded (Table II).

According to NCCN guidelines harmonised for SSA (Zelenetz *et al.*, 2019), we established an evaluation scheme for quality of pathological diagnosis and completeness of clinical diagnostic criteria. We revised availability of NHL subclassification, information on grade for unclassified NHL and diagnostic modality. We were unable to evaluate

Table II. Proportions of morphological subtypes within the non-Hodgkin lymphoma groups.

Lymphoma classification	ICD-O morphology codes	Patients, *n* (%)
All subclassified NHL		**217 (42.1)**†
Subclassified high-grade B cell NHL		**121 (55.8)***
Diffuse large B cell	9680, 9684	106 (48.8)*
Burkitt	9687	13 (6.0)*
Precursor lymphoblastic B cell	9728	1 (0.5)*
Plasmablastic	9735	1 (0.5)*
Subclassified low-grade B cell NHL		**64 (29.5)***
CLL/SLL	9823, 9670	40 (18.4)
Follicular	9690, 9695, 9698	12 (5.5)*
Marginal zone	9710, 9689, 9699	7 (3.2)*
Mantle cell	9673	3 (1.4)*
Lymphoplasmacytic	9671	2 (0.9)*
Subclassified T cell NHL		**15 (6.9)***
Anaplastic large T/Null cell	9714	5 (2.3)*
Mature T cell, NOS	9702	3 (1.4)*
Mycosis fungoides	9700	3 (1.4)*
Angioimmunoblastic T cell	9705	1 (0.5)*
Precursor T cell lymphoblastic	9729	1 (0.5)*
Natural killer/T cell	9719	1 (0.5)*
Sézary syndrome	9701	1 (0.5)*
Otherwise subclassified NHL		**17 (7.8)***
Composite Hodgkin and non-Hodgkin lymphoma	9596	8 (3.7)*
Precursor cell lymphoblastic, unknown cellular lineage	9727	8 (3.7)*
Disseminated Langerhans cell histiocytosis	9754	1 (0.5)*
All unclassified lymphoma		**299 (57.9)**†
Unclassified, graded NHL		**42 (8.1)**†
High-grade B cell, NOS	9591	4 (0.8)†
Low-grade B cell, NOS	9591	2 (0.4)†
High-grade, unknown cellular lineage, NOS	9591	24 (4.7)†
Low-grade, unknown cellular lineage, NOS	9591	12 (2.3)†
Unclassified NHL or lymphoma, not graded		**257 (48.6)**†
Unclassified NHL, NOS	9591	165 (32.0)†
Unclassified NHL or HL, NOS	9590	92 (17.8)†
Total cohort		**516 (100)**†

CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; HL, Hodgkin lymphoma; ICD-O, International Classification of Diseases for Oncology; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

*Percentage of all subclassified NHL.

†Percentage of total cohort.

immunohistochemistry (IHC) diagnostics or cytogenetics due to lack of consistent data. Furthermore, we revised availability of Stage, B symptoms, ECOG PS, HIV status and any imaging. Biochemical evaluation such as lactate dehydrogenase, full blood count, comprehensive metabolic panel and International Prognostic Index were not consistently available either.

We adjusted the proportion of the age-groups within our younger cohort to that of the Surveillance, Epidemiology and End Results (SEER) cohort 1975–2016 (Howlader *et al.*, 2019) (age-standardisation) to compare the lymphoma subtype distribution irrespective of the age-effect with the SEER cohort. For statistical analysis, we used the Statistical Package for the Social Sciences (SPSS®), version 25 (SPSS Inc., IBM Corp., Armonk, NY, USA).

Use of secondary data and ethical approval was granted in accordance with each registry's regulations and by Martin-Luther-University Halle-Wittenberg. The study protocol is in line with the Declaration of Helsinki.

Results

A total of 516 patients from 11 registries ranging between one patient (Cotonou) and 70 patients (Addis Ababa) were included. Clinical and pathology records could be traced for 293 (56.8%). We were able to trace clinical records of 293 patients. Completeness of our data is shown in Fig S1. We amended the most valid base of diagnosis for 51 patients. For 36 patients with clinical or unknown base of diagnosis only registered, we found cytological diagnosis for seven, and histological diagnosis for 29. For 15 patients with cytological diagnosis registered, we found histological diagnosis and amended base of diagnosis accordingly. After reviewing clinical and pathological records, we amended pathological diagnosis for 59 patients, and identified Working Formulation diagnoses in 41 patients with unclassified NHL. Of these, 34 were assigned to either high- or low-grade NHL, the remaining seven patients to unclassified NHL, NOS.

For 299 patients of the total cohort (57.9%) no subclassification was identified. Among these, 207 (69.2%) were unclassified NHL (ICD-O code 9591). For the other 92 (30.8%), diagnosis did not include distinction between NHL and Hodgkin lymphoma [ICD-O code 9590 (Malignant lymphoma, NOS)]. For these, diagnosis of Hodgkin lymphoma can thus not be ruled out, although this is far less likely than NHL due to its relatively lower incidence in SSA (Bray *et al.*, 2018). Subclassification was identified for 217 patients of the total cohort (42.1%). The diagnoses in the 516 patients were confirmed histologically in 76.2%, with FNAC only in 17.3% and clinically without specimen analysis in 6.5%. Histologically diagnosed cases were subclassified in 186 of 366 (50.8%), cytologically diagnosed cases in 31 of 83 (37.3%). No clinically diagnosed cases were subclassified.

In Fig 3, quality of pathological diagnosis stratified by PBCRs is shown. According to NCCN guidelines harmonised for SSA, we defined diagnosis as most precise when NHL subclassification was available. Reliability of subclassification was considered better for histological confirmation than for FNAC confirmation only. In the absence of subclassification,

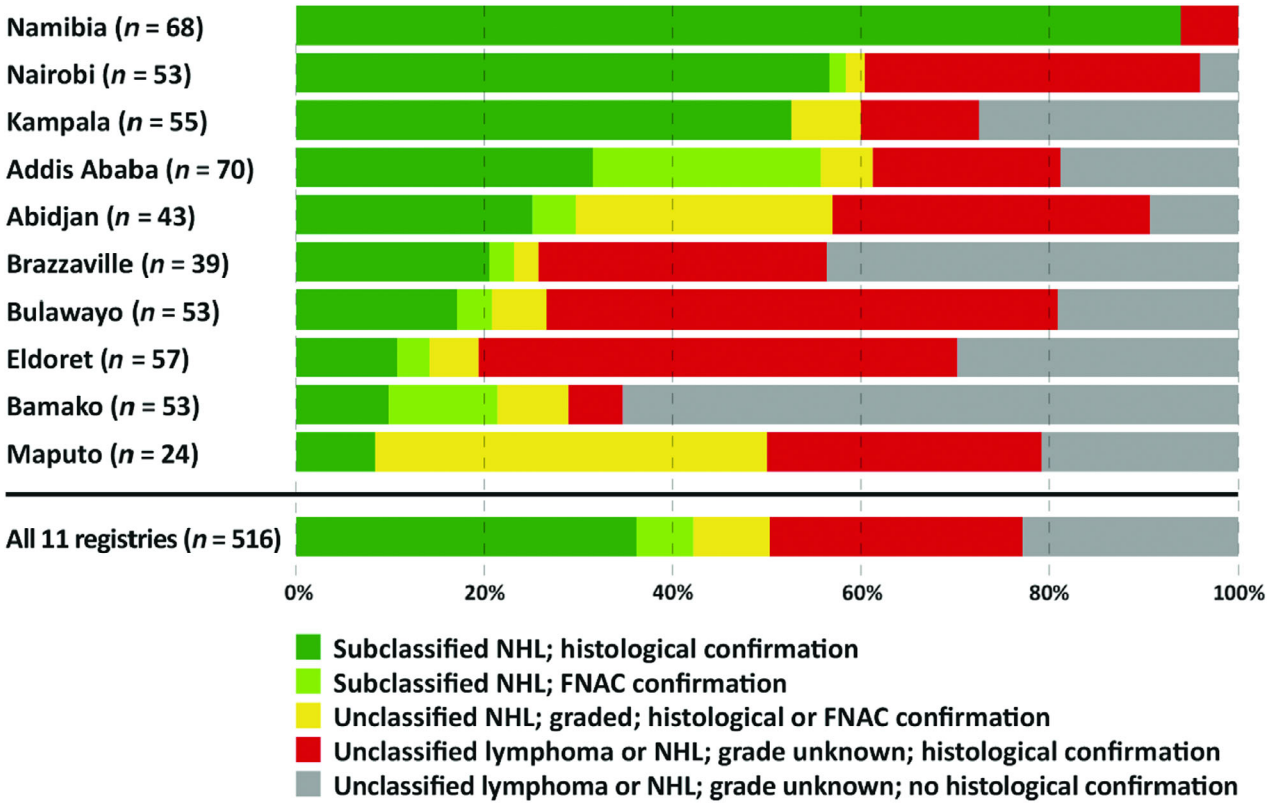


Fig. 3. Quality of pathological diagnosis. Stratified by population-based cancer registries, in order of quality of pathological diagnosis. With respect to non-Hodgkin lymphoma (NHL) subclassification, grade and diagnostic modality [according to National Comprehensive Cancer Network guidelines harmonised for Sub-Saharan Africa (Zelenetz *et al.*, 2019)]. Patients with morphologically ascertained diagnosis suitable for therapeutic decision-making (green and yellow): Patients with histopathological (dark green) or cytological (bright green) confirmation of subclassified NHL. Patients with unclassified but graded NHL (yellow). Patients with morphologically ascertained diagnosis not suitable for therapeutic decision-making (red): Patients with histological confirmation of lymphoma and neither subclassification nor grade. Patients with inconclusive diagnosis (white): Patients without histological confirmation of lymphoma and neither subclassification nor grade. (Cotonou was excluded from the figure due to small sample size, $n = 1$). FNAC, fine needle aspiration cytology. [Colour figure can be viewed at wileyonlinelibrary.com]

information on grade was deemed sufficient for basic therapy decision-making. For unclassified lymphoma with grade unavailable, histological confirmation of the disease was considered superior to other diagnostic modalities. In four registries, Namibia, Nairobi, Addis Ababa and Kampala, half or more NHLs were subclassified (94.1%, 58.5%, 55.7% and 52.7%, respectively). Bamako, Bulawayo, Eldoret and Maputo registries had the lowest proportion of NHLs subclassified (20.8%, 20.8%, 14.0% and 8.3%, respectively). Of the 299 unclassified cases, 123 (41.1%) were lacking histological confirmation.

Among the 217 subclassified NHLs, 20 subtypes were identified. We found a distribution of 55.8% high-grade B cell, 29.5% low-grade B cell, 6.9% T cell and 7.8% otherwise subclassified NHL. Diffuse large B cell lymphoma (DLBCL, ICD-O code 9680 and 9684) was the most common subtype (48.8%), followed by chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL, ICD-O code 9823 and 9670, 18.4%) and Burkitt lymphoma (BL, ICD-O code 9687, 6.0%). Rare entities such as various T cell NHL, primary central nervous system lymphoma (ICD-O code 9680), and extranodal unclassified lymphoma (ICD-O code 9590) suspicious of primary effusion lymphoma (ICD-O code 9678), were observed.

A moderate correlation between HIV prevalence in PBCRs and HIV-associated NHL was found (Table S2 and Fig S2). The proportion of HIV-associated NHL ranged between 38.5% and 89.1% in PBCRs with high HIV prevalence. For the remainder with lower prevalence, subtypes not associated with HIV were predominant.

Patients with high-grade B cell NHL had a median age of 43 years, patients with low-grade B cell NHL and T cell NHL were aged 52 and 56 years, respectively. When adjusting age-group proportions of our cohort to that of SEER, we found 41.4% DLBCL compared to SEER 27.8%, 25.4% for CLL/SLL compared to SEER 24.2% and 3.8% for BL compared to SEER 1.2% (Table S3).

Demographics, diagnostic modality and clinical presentation are shown in Table III. We found 88 of 473 NHLs to be primary extranodal lymphomas (18.6%) (Table S4).

Table III. Demographics, diagnostic modality and clinical presentation.

	High-grade B cell NHL	Low-grade B cell NHL	T cell NHL	All other lymphoma	Total cohort
Sex, *n* (%)					
Female	52 (41.6)	22 (33.3)	7 (46.7)	143 (46.1)	224 (43.4)
Male	73 (58.4)	44 (66.7)	8 (53.3)	167 (53.9)	292 (56.6)
Age, years					
Median (range) *n* (%)	43 (15–93)	52 (17–83)	56 (23–87)	42 (15–93)	45 (15–93)
15–39	50 (40.0)	15 (22.7)	4 (26.7)	133 (42.9)	202 (39.1)
40–59	56 (44.8)	24 (36.4)	5 (33.3)	119 (38.4)	204 (39.5)
≥60	19 (15.2)	27 (40.9)	6 (40.0)	58 (18.7)	110 (22.3)
Diagnostic modality, *n* (%)					
Histology	115 (92.7)	45 (73.8)	15 (100.0)	191 (68.2)	366 (76.2)
FNAC	9 (7.3)	16 (26.2)	0	58 (20.7)	83 (17.3)
Clinical	0	0	0	31 (11.1)	31 (6.5)
Unknown	1	5	0	30	36
Primary site involved, *n* (%)					
Nodal	97 (79.5)	36 (72.0)	8 (57.1)	244 (85.0)	385 (81.4)
Extranodal	25 (20.5)	14 (28.0)	6 (42.9)	43 (15.0)	88 (18.6)
Unknown	3	16	1	23	43
B symptoms*, *n* (%)					
No	9 (26.5)	2 (22.2)	2 (50.0)	6 (13.3)	19 (20.7)
Yes	25 (73.5)	7 (77.8)	2 (50.0)	39 (86.7)	73 (79.3)
Unknown	91	57	11	265	424
ECOG PS Score*, *n* (%)					
0 or 1	22 (40.7)	11 (64.7)	1 (33.3)	17 (29.3)	51 (38.6)
≥2	32 (59.3)	6 (35.3)	2 (66.7)	41 (70.7)	81 (61.4)
Unknown	59	49	12	252	384
Stage*, *n* (%)					
Early	22 (33.3)	4 (18.2)	3 (42.9)	19 (22.9)	48 (27.0)
Advanced	44 (66.7)	18 (81.8)	4 (57.1)	64 (77.1)	130 (73.0)
Unknown	59	44	8	227	338
HIV*, *n* (%)					
Negative	17 (29.8)	10 (76.9)	2 (66.7)	28 (34.6)	57 (37.0)
Positive	40 (70.2)	3 (23.1)	1 (33.3)	53 (65.4)	97 (63.0)
Unknown	68	53	12	229	362
Imaging*, *n* (%)					
CT/MRI/bone scan	17 (17.2)	4 (9.3)	2 (22.2)	13 (9.2)	36 (12.3)
X-ray and/or US	32 (32.3)	8 (18.6)	2 (22.2)	41 (28.9)	83 (28.3)
None	50 (50.5)	31 (72.1)	5 (55.6)	88 (62.0)	174 (59.4)
Unknown	26	23	6	168	223

CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FNAC, fine needle aspiration cytology; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; US, ultrasonography.

Stratified by high-grade B cell NHL [*n* = 125, including high-grade B cell NHL, not otherwise specified (*n* = 4)], low-grade B cell NHL [*n* = 66, including low-grade B cell NHL, not otherwise specified (*n* = 2)], T cell NHL (*n* = 15) and all other lymphoma (*n* = 310). Lugano Stage I, II, Binet Stage A and B were considered early disease, Lugano Stage III, IV and Binet Stage C advanced disease. We did not include patients with unknown clinical information in calculating percentage rates.

*Information for traced patients (*n* = 293) available only.

For 293 patients with clinical records traced, information on ECOG PS, B symptoms, Stage and HIV testing were available for 45.1%, 31.4%, 60.8%, and 52.6%, respectively. ECOG PS of ≥2 was documented in 61.4%, and 79.3% presented with B symptoms. In all, 73.0% were diagnosed with advanced Stage III or IV. HIV infection was documented for 63.0%. Imaging was done for 40.6%.

In Fig 4, quality of clinical diagnosis stratified by PBCRs is shown. According to NCCN guidelines harmonised for SSA, five clinical criteria are, among others, necessary for NHL diagnosis: ECOG PS, information on B symptoms, Stage, HIV status and any imaging done (Zelenetz *et al.*, 2019). Only 6.1% fulfilled all five criteria. On average 2.3 clinical criteria were available. Clinical diagnostics were most comprehensive in Kampala, with 9.1% meeting all five clinical criteria and on average 3.5 clinical criteria available. In Eldoret, Addis Ababa and Nairobi registries, clinical criteria were particularly lacking, with 1.7, 1.6 and 0.8 available on

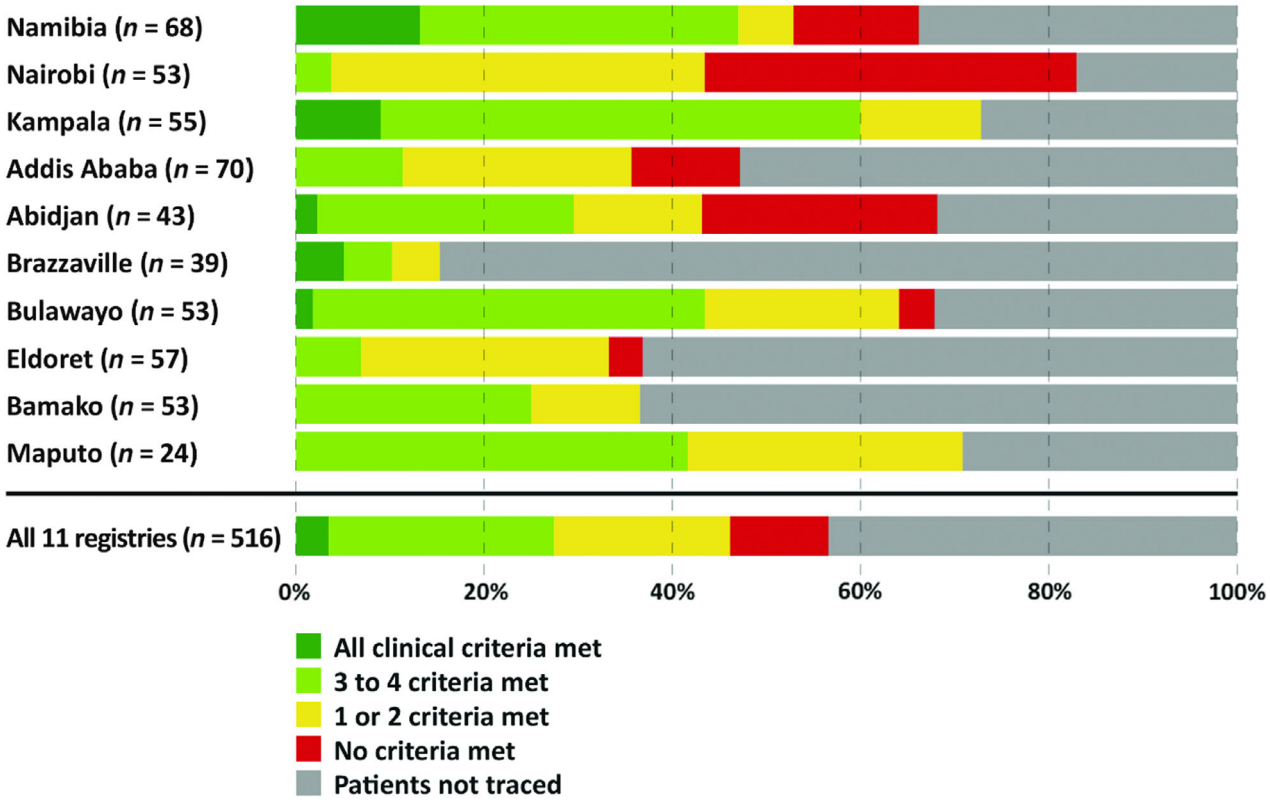


Fig. 4. Completeness of clinical diagnostic criteria. Stratified by population-based cancer registries, in order of Figure 3. With respect to information on Eastern Cooperative Oncology Group Performance Status, B symptoms, human immunodeficiency virus status, stage and any imaging [according to National Comprehensive Cancer Network guidelines harmonised for Sub-Saharan Africa (Zelenetz *et al.*, 2019)]. This information was only available for patients traced. (Cotonou was excluded from the figure due to small sample size, $n = 1$). [Colour figure can be viewed at wileyonlinelibrary.com]

average, respectively. Of the total cohort, 51.2% met two or fewer criteria only.

Discussion

Unclassified lymphoma cases and diagnostic modality

The NCCN has recognised the need to guide SSA physicians in resource-constrained settings and has published harmonised guidelines on a variety of B cell lymphomas (Zelenetz *et al.*, 2019). For the wide range of NHL entities, a broad spectrum of subtype-specific therapeutic algorithms has been designed. This requires NHL subclassification, as there are no recommendations on treatment of unclassified lymphoma. In this regard, the high proportion of 57.9% of unclassified lymphoma is striking. Distribution of unclassified lymphoma differed strongly among registries, ranging between Maputo (91.7%) and Namibia (5.9%). The varying quality of pathological diagnosis indicates that NHL diagnostic routine does not yet reach minimum standards for many patients. It is notable that for one in six patients, FNAC, and for one in 15 patients, clinical information only was the basis of the NHL diagnosis. Half of patients with NHL with histological confirmation had no subtype available, for patients with FNAC confirmation, the proportion was even higher (64.7%). The wide-spread use of FNAC in SSA has also been reported by others (Naresh *et al.*, 2011; Lemos *et al.*, 2018). FNAC is cheaper than core needle biopsy and much easier than surgical resection. However, as many investigators state, including the NCCN SSA guidelines, cytological diagnosis, let alone clinical presentation only, is deemed insufficient for NHL diagnosis except for CLL (Naresh *et al.*, 2011; Wilkins, 2011; Lemos *et al.*, 2018; Zelenetz *et al.*, 2019).

Biopsy material is mandatory for almost all kinds of pathological evaluation. Due to high cost and demanding infrastructure, IHC has yet to be facilitated in most SSA countries. Molecular genetics are practically unavailable. Consequentially, pathologists mostly rely on haematoxylin and eosin stains (Lemos *et al.*, 2018).

Hospital-based studies have reported much lower rates of unclassified lymphoma (13–14%) (Bateganya *et al.*, 2011; Milligan *et al.*, 2018). The severe lack of proper characterisation of lymphoma in our present cohort may be explained by lack of pathological infrastructure (Cainelli *et al.*, 2010; Wiggill *et al.*, 2013). Scarcity of trained personnel, especially

pathologists, is another major issue in SSA (Benediktsson *et al.*, 2007; Adesina *et al.*, 2013). In the Republic of Congo, for example, there is one pathologist available for the entire country with >4 million inhabitants (Jean-Félix Péko, 2019). The importance of correct classification of NHL remains an unmet need in SSA (Naresh *et al.*, 2011). Development and consistent implementation of resource-conserving guidelines on basic diagnostic procedures should be considered. The recent updates of the harmonised NCCN guidelines may lead to diligent and feasible subclassification algorithms for NHL in resource-constrained health systems. Hence, subtype-directed treatment could be enabled for a higher proportion of NHL. With limited resources, Malawian pathologists, for example, have reached concordance rates with American diagnoses of >90%, relying on basic cytology and histology services, a small IHC panel of nine antibodies and a telepathology conference (Montgomery *et al.*, 2016).

Subtypes of non-Hodgkin lymphoma

The relatively high percentage of high-grade B cell NHL (55.8%) observed in our present study confirms other studies from SSA (Naresh *et al.*, 2011; Wiggill *et al.*, 2011; Wiggill *et al.*, 2013; Patel *et al.*, 2015; Montgomery *et al.*, 2016; Perry *et al.*, 2016a; Milligan *et al.*, 2018). DLBCL (ICD-O code 9680 and 9684), BL (ICD-O code 9687), plasmablastic lymphoma (ICD-O code 9735), primary central nervous system lymphoma (ICD-O code 9680), and unclassified extranodal lymphoma suspicious of primary effusion lymphoma (ICD-O code 9678) were observed. All of these aggressive subtypes mentioned are associated with HIV (Re *et al.*, 2019), partly explaining their high proportion in our present study. However, in other parts of the resource-constrained world with much lower HIV prevalence than SSA, high-grade B cell NHLs are also known to be frequent. High-grade B cell NHL incidence is lower in the multicentric, population-based SEER study (31.3%) (Howlader *et al.*, 2019). This indicates that besides higher burden of further infectious diseases such as EBV (Crawford *et al.*, 2014), environmental and other factors such as demographics may play a role as well (Perry *et al.*, 2016a).

However, we could show that when age-adjusting our present cohort to the SEER cohort (Howlader *et al.*, 2019), proportions of DLBCL and BL remained lower in the SEER cohort (DLBCL adjusted: 41.4%, SEER: 27.8%; BL adjusted: 3.8%, SEER: 1.2%, respectively). HIV prevalence varied across the 11 participating PBCRs. Nairobi, Abidjan, Kampala, Namibia, Bulawayo and Maputo had high HIV prevalence (4.9–16.9%); whereas prevalence for the remaining PBCRs was much lower (1.7–4.1%) (National AIDS and STI Control Programme (NASCOP), 2012; United Nations Joint Programme on HIV/AIDS (UNAIDS), 2018; The Demographic and Health Surveys (DHS) Program, 2019). This affects proportions of HIV-associated lymphoma (89.1% in Namibia, 64.5% in Nairobi, 51.7% in Kampala *versus* 25.6% in Addis Ababa and 27.3% in Bamako). When testing for heterogeneity, Fig S2 shows that HIV prevalence in registries did moderately correlate with the respective proportion of HIV-associated NHL. There are numerous reasons that may increase or decrease the ratio of HIV-associated NHL in respective registries with varying HIV prevalence, including availability and reliability of detailed diagnosis, stigma of HIV-infected patients and quality of service for HIV patients.

The low frequency for CLL/SLL is consistent with other studies on NHL subtype distribution in SSA (Wiggill *et al.*, 2011; Perry *et al.*, 2016a) When age-adjusting to the SEER cohort, however, the proportion of CLL/SLL approximated the SEER proportion (CLL/SLL adjusted: 25.4%, SEER: 24.2%). Patients diagnosed with high-grade B cell NHL were diagnosed at a young age (median 43 years) compared to low-grade B cell NHL and T cell NHL patients (median age 52 and 56 years, respectively). The high burden of young patients diagnosed with aggressive NHL represents a socioeconomic threat and efficient treatment could reduce impact on SSA economies. Prospective, hospital-based studies in HIV-prevalent settings have shown that treatment for NHL can be safe, effective and feasible. The 1-year overall survival, regardless of NHL subtype, in Botswana was 53.7%. For DLBCL in Malawi, the 2-year progression-free survival was 34% (Milligan *et al.*, 2018; Painschab *et al.*, 2019)."

Clinical presentation

Patients with NHL in SSA present late, with nearly three-quarters diagnosed at advanced stage, almost two-thirds scoring an ECOG PS of ≥2, and four out of five suffering from B symptoms in our present cohort. Results are comparable to another retrospective, hospital-based study from the Uganda Cancer Institute (Bateganya *et al.*, 2011). The issue of late disease recognition due to lack of diagnostic resources, misdiagnosis (Buyego *et al.*, 2017), poor referral mechanisms, financial woes, low awareness and poverty may add to late presentation in the SSA tertiary hospital setting (Mwamba *et al.*, 2012). Even in Botswana, a middle-income country, duration between initial NHL symptoms and eventual diagnosis of NHL was 280 days on average (Milligan *et al.*, 2018). The proportion of primary extranodal disease was 18.6% in our present cohort. Even after carefully reviewing clinical records, our present data on extranodal organ manifestation of NHL may be confounded by primary nodal NHL infiltrating extranodal organs. Patients with extranodal lymphoma were possibly not diagnosed due to lack of comprehensive imaging such as computed tomography, let alone positron emission tomography, and absence of imaging in 59.4% of traced patients. However, in case of doubt, we assigned NHL as primary nodal rather than extranodal disease. Moreover, lack of imaging may also lead to understaged NHL within our present cohort, for which more sophisticated staging would have revealed even more advanced disease stages. A review has reported classification

of primary extranodal lymphoma to be inconsistent on a global scale (Vannata & Zucca, 2015), which may impede comparability with other studies in SSA. Mostly, these studies have reported higher proportions of extranodal disease; however, they did not specify whether extranodal disease was primary or secondary (Mwamba *et al.*, 2012).

In the absence of imaging procedures like ultrasonography, X-ray, and even less available higher-cost imaging procedures, thorough physical examination is essential. We found a high proportion of traced patients that lacked imaging and staging (59.4%, and 39.2%). Furthermore, lack of HIV testing in 139 patients (47.4% of 293) has to be noted. Due to these shortfalls, a median of only 2.3 of the five baseline non-pathological diagnostic criteria recommended by the harmonised NCCN guidelines were available. Stage, HIV status, and ECOG PS are key determinants for treatment. Improving completeness of patient examination could enhance personalised therapy decision-making and outcome.

Strengths and limitations of our study

The present study has several strengths. First, our initial total population-based cohort ($n = 599$) comprised 56.1% of all 1068 patients with NHL registered in the 11 PBCRs during the period of randomisation, of which we traced the clinical records of 293 patients. Second, the geographical variety of countries allows for an overview of patients with NHL with different ethnicities living in different socioeconomic settings, with both high and low HIV and malaria prevalence. Third, the patients were a random sample of all adult NHL cases, from both public and private institutions, treated or untreated, and we considered all bases of diagnosis, whether made histologically or solely clinically. The present study is, in fact, the first population-based overview of clinical presentation and diagnostics of patients with NHL in real-world SSA.

The present study also has several limitations. First, population-based cancer registries are limited by data quality (Parkin *et al.*, 2018). For example, 52 patients (8.7%) that were registered as NHL in the PBCR databases did not actually have a NHL diagnosis in their clinical records. For patients with traced clinical records (56.8%), we could amend these shortfalls and exclude such patients. Second, all of the PBCRs with the exception of Namibia cover urban populations and do not reflect experience in rural areas (Crocker-Buque & Pollock, 2015), but they provide the broadest image available of NHL patients' reality across the 10 countries participating. Third, we expect misclassified lymphoma in our present cohort. Deviations between diagnosis of general pathologists and expert haemato-pathologists are common in SSA, but occur also in high-income settings (Clarke *et al.*, 2004; LaCasce *et al.*, 2008; Chang *et al.*, 2014; Herrera *et al.*, 2014), including assignment to wrong cellular lineage (Armitage, 2013; Herrera *et al.*, 2014; Lage *et al.*, 2015) or even confounding benign and malignant disease (Wilkins, 2011; Ayers *et al.*, 2012; Masamba *et al.*, 2016; Buyego *et al.*, 2017). Two expert re-evaluations of lymphoma tissue in SSA have described diagnostic accuracy of 75% and 78%, respectively, reporting on poor tissue quality and frequent misdiagnoses (Naresh *et al.*, 2011; Ogwang *et al.*, 2011). Fourth, results on subtypes reported in our present study are hampered by different classification systems as outdated as the Working Formulation. We consider subtype distribution within our present cohort reliable nonetheless because we only considered outdated lymphoma subclassifications that allowed for obvious conversion to the current classification system. Fifth, a major issue to data analysis represented the rate of clinical records traced, 56.8%. We believe that clinical records were either, missing at random because of handwritten records, misspelling of names and inconsistent archive quality, or missing when records were not initiated in patients without clinical therapy. Even when clinical records could be assessed, we found a high proportion of missing data. However, this seems to be a general problem in the SSA setting as in a single-centred retrospective study and even in another multicentre prospective study, Stage was missing for 40% and 28% of patients, respectively (Bateganya *et al.*, 2011; Milligan *et al.*, 2018).

Conclusion

Our present pilot study describes NHL subtype distribution and diagnostic service received for patients on a population-level. As both pathological, as well as clinical diagnostics, are incomplete in most patients, thorough implementation of the NCCN guidelines harmonised for SSA remains challenging in many countries. Development of diagnostic algorithms emphasising feasibility in resource-constrained settings, improvement of laboratory infrastructure (especially IHC), and training of pathology and oncology workforce is required for more accurate diagnosis. Only then can sensible decision-making on guideline-adherent treatment be implemented for patients with NHL in SSA. The effect of such measures in real-world SSA should be monitored applying population-based research.

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Author contributions

All authors contributed to the contents and revised the article. Annelle Zietsman, Jean-Félix Péko, Fisihatsion Tadesse, Nathan G. Buziba, Henry Wabinga, Mary Nyanchama, Margaret Z. Borok, Mamadou Kéita, Guy N'da, Cesaltina F. Lorenzoni and Marie-Thérèse Akele-Akpo were responsible for the provision of data. Nikolaus C.S. Mezger and Eva J. Kantelhardt designed the study, did the data analysis, interpreted the data, and wrote the article. Cornelia Gottschick, Mascha Binder, Jörg Mezger, Ahmedin Jemal, Donald Maxwell Parkin and Claudia Wickenhauser did the data analysis, interpreted the data and wrote the article. Mirko Griesel, Lucia Hämmerl, Tobias P. Seraphin, Jana Feuchtner, interpreted the data.

Conflicts of interest

The authors declare no competing financial interests. Eva J. Kantelhardt has received travel support from Daiichy Sankyo.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Completeness of data. All areas relative to black rectangle (NHL patients registered, n = 1068). Red: pathological (cytological or histological) confirmation of NHL *only*; yellow: any clinical data on HIV, stage, ECOG PS B symptoms or imaging *only*; orange: *both* pathological confirmation of NHL *and* any clinical data present. For patients not traced (n = 223), only registry data on demographics and pathological diagnosis were available. For these, no data on clinical information on stage, HIV status etc. were available. ECOG PS, Eastern Cooperative Oncology Group Performance Status; NHL, non-Hodgkin lymphoma.

Fig S2. Correlation between HIV prevalence for PBCR and HIV-associated NHL among subclassified NHL. Correlation coefficient was r = 0,605 (p value = 0.064). HIV prevalence for 15-49 year old populations was extracted from online data bases (National AIDS and STI Control Programme (NASCOP), 2012; United Nations Joint Programme on HIV/AIDS (UNAIDS), 2018; The Demographic and Health Surveys (DHS) Program, 2019). PBCR, population-based cancer registry; NHL, non-Hodgkin lymphoma.

Table S1. ICD-10 codes included in study for patient selection (April *et al,* 2013).

Table S2. Proportion of HIV-associated non-Hodgkin lymphoma among subclassified non-Hodgkin lymphoma. Stratified by registry and HIV prevalence. HIV prevalence for 15-49 year old populations was extracted from online data bases (National AIDS and STI Control Programme (NASCOP), 2012; United Nations Joint Programme on HIV/AIDS (UNAIDS), 2018; The Demographic and Health Surveys (DHS) Program, 2019).

Table S3. Age-adjustment of non-Hodgkin lymphoma (NHL) subtypes found in our cohort to Surveillance, Epidemiology and End Results (SEER) cohort 1975-2016 (Howlader *et al,* 2019). Age 15-19 in our cohort (n=27) and 0-19 in SEER cohort (n=14.312) were excluded for analysis. Subsequently, unclassified NHL (International Classification of Diseases for Oncology (ICD-O) morphology code 9591 (April *et al,* 2013)) and unclassified lymphoma or NHL (9590) were excluded for our cohort (n=272) and for SEER (n=11.752) when calculating proportions.

Table S4. Primary extranodal lymphoma. Stratified by topographic categories (April *et al,* 2013) and lymphoma types.

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Original Article

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;0:1-12**.

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

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See editorial on pages 1-2, this issue.

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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 prolon

g 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

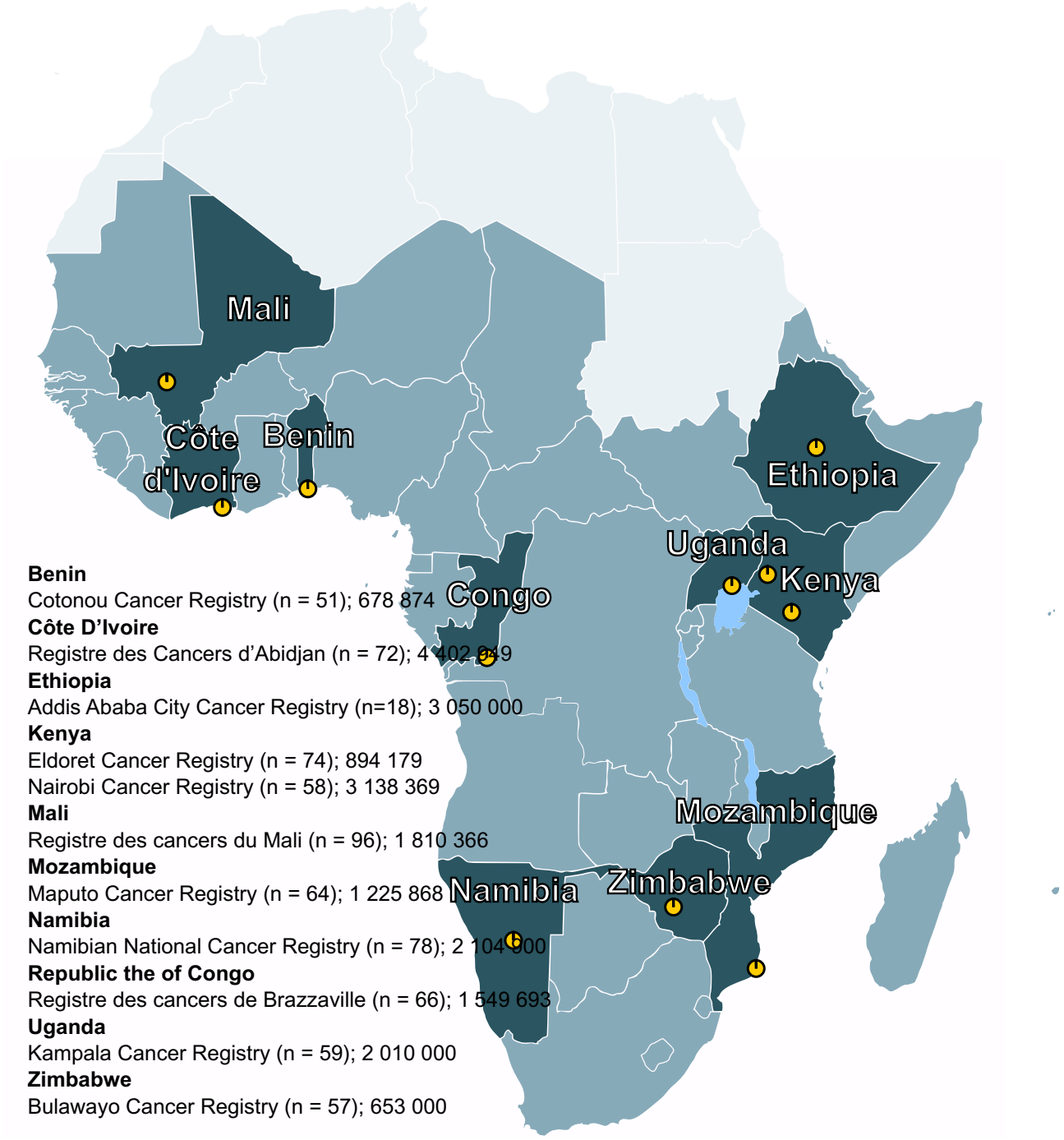

Figure 1. Countries of participating cancer registries. Countries of participating population-based cancer registries are highlighted along with the names of the registries, the number of included patients (n), and the population of each coverage area (persons).

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.

[a]Part of the total population-based cohort for which medical records were not available.

[b]Part of the total population-based cohort for which medical records were available (additional clinical information).

[c]Subgroup 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).

[d]Subgroup 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).

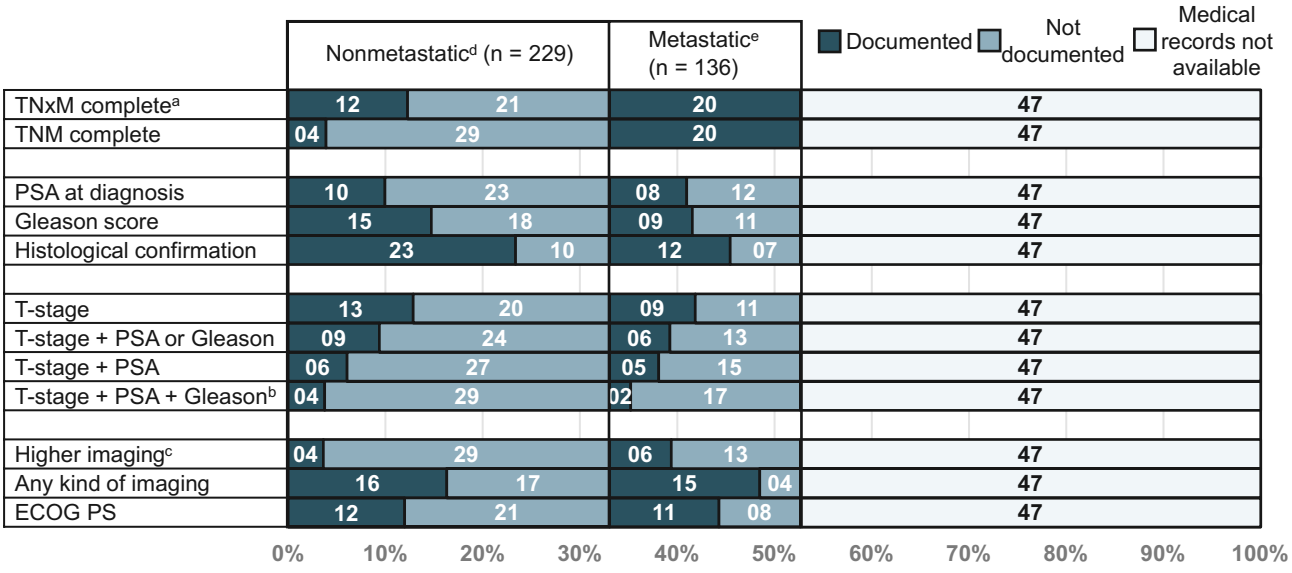

Figure 2. Availability of diagnostic information for patients with prostate cancer in the total population-based cohort (n = 693). [a]Nx included. [b]Main prognostic factors according to the 2017 National Comprehensive Cancer Network guidelines. [c]For example, computed tomography, magnetic resonance imaging, or a bone scan (used for staging). [d]The 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). [e]The 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.

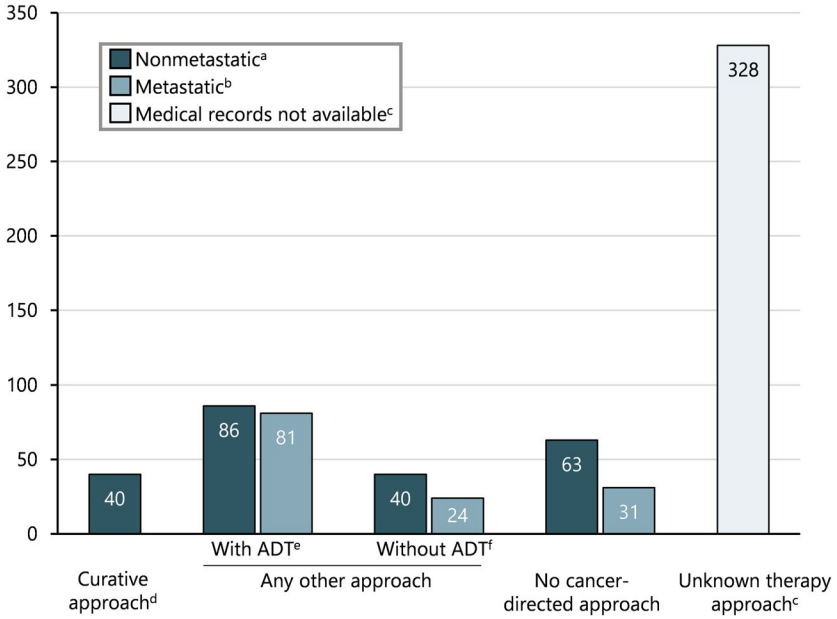

Figure 3. Primary treatment approach by identified M stage in the total population-based cohort (n = 693). [a]The nonmetastatic subgroup (n = 229) comprised all patients without a pathological or clinical suggestion of metastasis (M0), including patients with an unknown lymph node status (Nx M0). [b]The 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). [c]No medical records were available for the extraction of clinical data (n = 328). [d]Radical prostatectomy or external-beam radiation therapy with a potentially curative dose. [e]ADT 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. [f]Transurethral resection of the prostate or external-beam radiation therapy with a palliative dose or chemotherapy without ADT. ADT indicates androgen deprivation therapy.

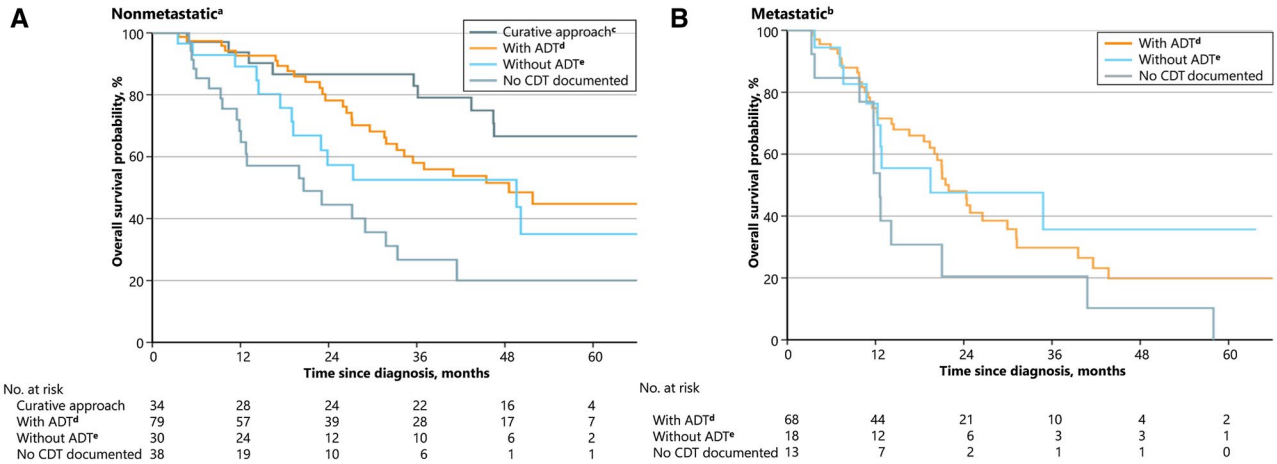

Figure 4. Overall survival of patients from the traced cohort with at least 3 months of survival stratified by M stage: differences according to the treatment approach. [a]These patients surviving at least 3 months from the nonmetastatic subgroup (n = 181) included all patients without a pathological or clinical suggestion of metastasis (M0), including patients with an unknown lymph node status (Nx M0). [b]These 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). [c]Radical prostatectomy or external-beam radiation therapy with a potentially curative dose. [d]Any other approach with ADT by surgical or medical castration. [e]Any 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 ≥ 2" (HR, 5.64; 95% CI, 2.46-12.94) were associated with a significantly

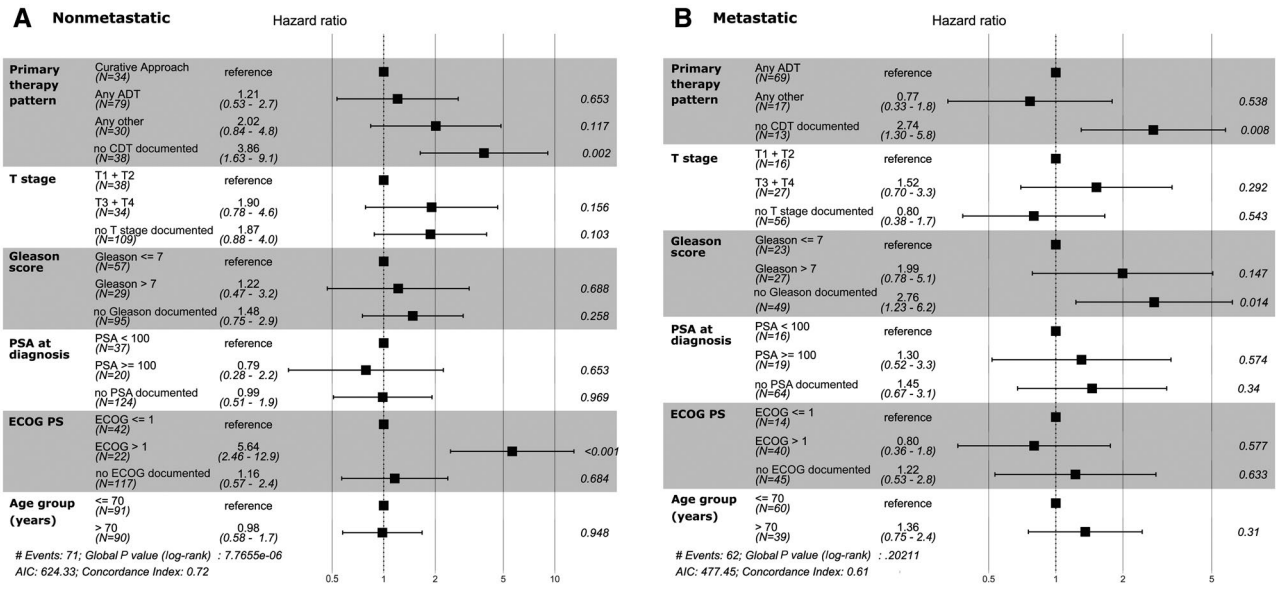

Figure 5. Forest plots showing the influence of primary treatment patterns on the survival of (A) patients with nonmetastatic prostate cancer[a] and (B) patients with metastatic prostate cancer.[b] The hazard ratios and 95% confidence intervals are the results of a multivariable Cox regression model adjusted for the T stage, Gleason score, PSA at diagnosis, ECOG PS, and age group. [a]These 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). [b]These 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 nonmetastatic 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 Feuchtner:** 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. **Sévérin 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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Leipzig, der 16. August 2022 Jana Cathrin Feuchtner

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