Das Zervixkarzinom in Subsahara-Afrika: Eine multinationale populationsbasierte Kohortenstudie zu Therapiequalität und Überleben

Dissertation

zur Erlangung des akademischen Grades
Doktor der Medizin (Dr. med.)

vorgelegt
der Medizinischen Fakultät
der Martin-Luther-Universität Halle-Wittenberg

von Mirko Griesel

Betreuer*in: Prof.in Dr.in med. Eva J. Kantelhardt

Gutachter*innen:

Prof. Dr. Dirk Vordermark, Halle (Saale)

Prof.in Dr.in Bahriye Aktas, Leipzig

Datum der Verteidigung: 13.06.2024

Referat

Einführung: Das Zervixkarzinom ist in vielen Ländern Subsahara-Afrikas (SSA), die alle zu den Ländern mit niedrigem oder mittlerem Einkommen (LMIC) gehören, die häufigste Krebserkrankung bei Frauen. Die Überlebensrate ist im globalen Vergleich niedrig, aus der Makroperspektive sind Hindernisse für eine adäquate Behandlung bekannt. Deshalb sollte die Therapiequalität sowie ihr Zusammenhang mit dem Gesamtüberleben (overall survival: OS) auf Populationsebene anhand individueller Daten in mehreren afrikanischen Ländern untersucht werden.

Methoden: Auf Grundlage einer eigenen Pilotstudie in Addis Abeba (Äthiopien) wurden in dieser retrospektiven Beobachtungsstudie in neun populationsbasierten Krebsregistern in acht Ländern (Äthiopien, Benin, Elfenbeinküste, Kenia, Mali, Mosambik, Uganda und Simbabwe) zufällig 632 Patientinnen aus 2010-2016 ausgewählt. Die Therapie wurde auf Adhärenz zur Leitlinie des National Comprehensive Cancer Network 2010 untersucht und die Assoziation mit dem OS mit multipler Cox-Regression modelliert.

Ergebnisse: 15,8 % der 632 Patientinnen erhielten eine Cancer-directed therapy (CDT) mit kurativem Potenzial (5,2 % strikt leitlinientreu, 2,4 % mit kleineren und 8,2 % mit größeren Abweichungen). Bei 22 % hatte die CDT kein kuratives Potential oder es war gar keine CDT dokumentiert. 15,7 % wurden im Stadium IV diagnostiziert. Bei 46,9 % war keine Therapiebewertung möglich: 11,9 % fehlte das Stadium oder eine ausreichende Nachbeobachtung, bei 35,1 % konnten keine Krankenakten gefunden werden. Am häufigsten leitlinientreu war die Behandlung in Nairobi (49 %), am seltensten in Maputo (4 %). Im Stadium I-III und bei ausreichender Nachbeobachtung waren kleinere (Hazard Rate Ratio [HRR], 1,73; 95-%-Konfidenzintervall [KI]: 0,36-8,37) und größere (HRR, 1,97; KI, 0,59-6,56) Abweichungen mit einem niedrigeren OS verbunden. CDT ohne kuratives Potenzial (HRR, 3,88; KI: 1,19-12,71) und keine CDT (HRR, 9,43; KI: 3,03-29,33) waren mit wesentlich schlechterem Überleben assoziiert.

Schlussfolgerung: Diese populationsbasierte Studie stellt als erste ihrer Art in SSA fest, dass die meisten Patientinnen keinen Zugang zu adäquater Behandlung haben: Im schlechtesten Fall erhielten zwei Drittel trotz heilbarer Stadien nie eine CDT, was mit deutlich geringerem Überleben verknüpft war. Für die Praxis könnte es Behandlungsoptionen geben, die nicht strikt leitlinientreu sind, aber einen relevanten Überlebensvorteil bieten, während andere nicht-kurative Therapien gänzlich vermieden werden sollten. Für Entscheidungsträger*innen ist wesentlich, dass mehr Strahlentherapiekapazitäten und gynäkologische Onkolog*innen benötigt werden.

Griesel, Mirko: Das Zervixkarzinom in Subsahara-Afrika: Eine multinationale populationsbasierte Kohortenstudie zu Therapiequalität und Überleben, Halle (Saale), Univ., Med. Fak., Diss., 24 Seiten, 2024

Abstract

Introduction: Cervical cancer is the most common cancer among females in many Sub-Saharan African (SSA) countries, all of which are low- or middle-income countries. Survival is relatively low and hindrances to adequate care are known at the macro perspective. We have therefore assessed adherence to treatment guideline and its association with overall survival (OS) on individual patient level in different SSA cancer registries.

Methods: Based on the experience from a pilot study in Addis Ababa, Ethiopia, in this observational retrospective longitudinal study we included randomly sampled 632 patients from 2010-1016 from nine population-based cancer registries in eight countries: Benin, Ethiopia, Ivory Coast, Kenya, Mali, Mozambique, Uganda, and Zimbabwe. Cancer-directed therapy (CDT) was evaluated for adherence to the 2010 guidelines of the National Comprehensive Cancer Network. The degree of association with OS was modelled with multiple Cox regression.

Results: Out 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 either without curative potential or not documented at all 22 %; 15.7 % were diagnosed with stage IV disease. Adherence assessment was not feasible in 46.9 %: stage or sufficient follow-up were missing in 11.9 %, and records could not be traced in 35.1 %. The most guideline-adherent cases were in Nairobi (49 %) and the fewest were in Maputo (4 %). In FIGO stage I-III (n=190) and with sufficient follow-up, minor and major guideline deviations were linked to lower OS (hazard rate ratio [HRR], 1.73; 95 % confidence interval [CI], 0.36-8.37 and 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) were associated with substantially worse survival.

Conclusion: This study warns about the lack of access to timely and high-quality diagnostic and treatment services, which most patients experience: approximately one in six patients with cervical cancer in SSA received CDT with curative potential. Around two thirds of women never received CDT despite curable disease stages, which was associated with lower OS. Regarding clinical practice, there might be CDT options that, although not fully guideline-adherent, have relevant survival benefits while others should be avoided. Investments in infrastructure (radiotherapy) and personnel (surgical training) are necessary to improve OS.

Griesel, Mirko: Das Zervixkarzinom in Subsahara-Afrika: Eine multinationale populationsbasierte Kohortenstudie zu Therapiequalität und Überleben, Halle (Saale), Univ., Med. Fak., Diss., 24 Seiten, 2024

Inhaltsverzeichnis

Abürzungsverzeichnis

a	Jahr
AFCRN	African Cancer Registry Network
AIDS	Acquired Immunodeficiency Syndrome
ASRS	Age-standardised relative Survival
CDT	Cancer-directed therapy
EBRT	External beam radiotherapy
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
HIC	High-income country
HIV	Humanes Immundefizienz-Virus
HPV	Humanes Papillomvirus
HRR	Hazard rate ratio
IAEA	International Atomic Energy Agency
IARC	International Agency for Research on Cancer
KI	95-%-Konfidenzintervall
LIC	Low-income country
LMIC	Low- and middle-income countries
mm	Millimeter
NCCN	National Comprehensive Cancer Network
OS	Overall Survival
SEER	Surveillance, Epidemiology, and End Results Program
SSA	Subsahara-Afrika
UICC	Union for International Cancer Control
USA	United Steates of America

1. Einleitung und Zielstellung

1.1. Vorbemerkung zur geschlechtersensiblen Schreibweise

Die „Empfehlungen zur geschlechtersensiblen Sprache“ der Universitätsmedizin Halle liegt dieser Dissertationsschrift zugrunde und der Autor ist von der Sinnhaftigkeit einer differenzierten inklusiven Schreibweise überzeugt.[1] Es wurde jedoch der Kompromiss eingegangen, bei den Betroffenen des Zervixkarzinoms noch die binären Begriffe Mädchen, Frauen und Patientinnen zu verwenden, obwohl die wesentliche Voraussetzung für die Entwicklung des Zervixkarzinoms lediglich das Vorhandensein der Zervix uteri ist. Dies ist auch bei Menschen mit anderen Geschlechtsidentitäten möglich.

1.2. Krebs und seine bevölkerungsbasierte Überwachung

Krebserkrankungen sind weltweit ein häufiger Grund für Krankheit und Tod. In Ländern mit mittleren und geringen Einkommen (Low- and middle-income countries: LMIC) sind sie auch ein Grund für Armut.

Das Auftreten von Krebserkrankungen ist abhängig von Faktoren wie Alter und genetischer Veranlagung, unterliegt aber auch Umwelteinflüssen. Einmal erkrankt, sind Heilungschancen abhängig vom Zugang zu adäquater Diagnostik und Therapie, der insbesondere in Ländern mit geringem Einkommen stark eingeschränkt sein kann.[2]

Wegen der immensen individuellen wie auch systemischen (vgl. *1.3.2 Soziales*) Bedeutung von Krebserkrankungen sind weltweit an ausgewählten Zentren bevölkerungsbasierte Register etabliert, die Daten zu Anzahl und Schwere von Krebserkrankungen, aber auch zur Behandlung und der Überlebensdauer aller Bewohner*innen eines Gebiets liefern können. Auf der Basis dieser Informationen lassen sich bedarfsgerecht Präventionsmaßnahmen für bestimmte Personengruppen und onkologische Versorgungsstrukturen planen sowie deren Erfolge im zeitlichen Verlauf beobachten.[3]

Bevölkerungsbasierte Krebsregistratur ist weltweit heterogen organisiert und finanziert, wobei es erhebliche Unterschiede in der Verfügbarkeit und Qualität von flächendeckenden Krebsdaten gibt. Zum Teil sind diese leider mangelhaft. Dies trifft im Besonderen auf das subsaharische Afrika (SSA) zu, wo 2015 in 20 von 46 Staaten gar keine populationsbasierten Register existierten und in den übrigen Staaten 19 von 26 Registern weniger als fünf von 15 Qualitätskriterien erreichten.[4] In dieser Region leistet das African Cancer Registry Network (AFCRN),[5] eine Nichtregierungsorganisation im

Auftrag der Internationalen Krebsforschungsagentur (IARC), Unterstützung bei Aufbau, Ausbildung und Datenauswertung und ist zusammen mit den jeweiligen nationalen oder lokalen Registern wesentliche Quelle für im Folgenden zitierte Daten wie auch Kooperationspartner bei dieser Arbeit.

1.3. Krebs in Subsahara-Afrika

Unter Subsahara-Afrika wird eine Gruppe von 48 Staaten verstanden, die in wirtschaftlichem und kulturellem Austausch stehen. Sie haben außerdem gemein, dass sie der Gruppe der Low- and middle-income countries der Weltbank angehören – mit Ausnahme der Seychellen.[6] In dieser Region leben rund 1,1 Milliarden Menschen mit einer Lebenserwartung von aktuell rund 62 Jahren, welche noch deutlich unter der der Vereinigten Staaten von Amerika (USA) mit 77 Jahren liegt.[7][8] Allerdings ist ein deutlicher Trend abzusehen bei der Entwicklung von Lebensgewohnheiten, Wohlstand und Lebenserwartung, der eine Verschiebung der wesentlichen Belastungen der subsaharischen Gesundheitssysteme von übertragbaren hin zu nicht-übertragbaren Krankheiten mit sich bringt: Neben Erkrankungen aus dem metabolischen und kardiovaskulären Bereich steigen die Inzidenzraten von Krebserkrankungen, deren Diagnose und Therapie sehr aufwändig und kostenintensiv sind.[9] Dabei können in SSA onkologische Standards bei Prävention, Diagnostik und Therapie schon jetzt oft nicht umgesetzt werden, [10] was zu bis vierfach erhöhten Mortalitätsraten bei einzelnen Krebsentitäten führt und die ohnehin stark belasteten Gesundheitssysteme der Region vor massive Herausforderungen stellt.[11] Dabei haben in SSA nach Altersstandardisierung bei Frauen das Mammakarzinom mit 37,8, das Zervixkarzinom mit 32,2 und das Kolon-/Rektumkarzinom mit 7,1/100.000/Jahr(a) sowie bei Männern das Prostatakarzinom mit 35,4, das Kolon-/Rektumkarzinom mit 9,0 Leberkarzinom mit 8,5/100.000/a die höchsten Inzidenzraten.[12] Im Vergleich zu den anderen genannten Malignomen hat das Zervixkarzinom biologische, diagnostische, therapeutische und soziale Besonderheiten. Aus diesem Grund soll es wesentlicher Gegenstand der vorgelegten Arbeit, einer multinationalen populationsbasierten Untersuchung von Therapiequalität und Überleben, sein.

1.4. Zervixkarzinom in Subsahara-Afrika

1.4.1. Biologie

Das Zervixkarzinom weist biologische Eigenschaften auf, die es aus präventiver Sicht besonders interessant machen: Es ist etabliert, dass beinah alle Zervixkarzinome aufgrund einer Infektion mit Hochrisiko-Subtypen des Humanen Papillomvirus (HPV) entstehen.[13] Während der Karzinogenese können zytologische Untersuchungen, die

seit der zweiten Hälfte des 20. Jahrhunderts zur Verfügung stehen, Aufschluss über Schwere der Virusinfektion und maligne Zelltransformation geben. Durch verschiedene Therapieoptionen von prä-malignen Läsionen (z.B. Kryotherapie, Schlingenexzision) kann die Entstehung eines invasiven Karzinoms verhindert werden. Seit Beginn des 21. Jahrhunderts ist es möglich, mit Totimpfstoffen die Anzahl der Infektionen mit den häufigsten karzinogenen HPV-Subtypen deutlich zu senken.[14] Sind Frauen zusätzlich von einer Infektion mit dem Humanen Immundefizienz-Virus (HIV) betroffen, könnte eine adäquate antiretrovirale Therapie dem Auftreten des Zervixkarzinoms entgegenwirken, das seinerseits eine der Erkrankungen ist, die das Endstadium einer HIV-Infektion, das Acquired Immunodeficiency Syndrome (AIDS), definieren.[15] Diese wirkungsvollen Angriffspunkte für Prävention unterscheiden das Zervixkarzinom von vielen anderen Krebsarten.

1.4.2. Soziales

Wirkungsvolle Möglichkeiten zur Prävention sind vorhanden. Im Folgenden soll die Notwendigkeit der Prävention oder zumindest der Diagnose in frühem Stadium begründet sowie die Folgen selbst zu zahlender Therapie beleuchtet werden.

Das Zervixkarzinom trifft Frauen häufig in Phasen ihres Lebens, in denen sie in ihren sozialen Netzen tragende Rollen spielen – so zum Beispiel Lohnarbeit und Haushaltsarbeit sowie Geburt, Pflege und Erziehen von Kindern.[16] Eine insbesondere in fortgeschrittenen Stadien kostenintensive und aufwändige Therapie belastet nicht nur afrikanische Gesundheitssysteme, sondern bei weitgehender Abwesenheit von universeller Absicherung gegen Krankheitskosten in SSA auch die finanzielle Lage und sozialen Netze der einzelnen Patientinnen massiv.[17] Für Argentinien als ein Middle-income country außerhalb von SSA ist berichtet, dass sogar trotz Krankenversicherung die Verdienstausfälle in der Familie zum Verkauf von Eigentum, Aufbrauchen von Erspartem und gar Rationierung von Lebensmitteln führten.[18] Trotz oder teils gar wegen Therapieversuchen ist das Zervixkarzinom ein bedeutsamer Grund für sogenannte „verlorene Lebensjahre“ und „durch Behinderung eingeschränkte Lebensjahre“ und Stigmatisierung für Frauen in SSA, während es in Ländern mit hohem Einkommen (High-income countries, HIC) eine deutlich untergeordnete Rolle spielt.[16][19]

Die negativen sozialen Implikationen des Zervixkarzinoms sind also schwerwiegend. Dies soll im Folgenden ergänzt werden durch eine quantitative epidemiologische Beschreibung des Zervixkarzinoms in SSA kontrastiert durch Vergleiche mit HIC. So soll

zum einen die Dimension des Problems in SSA verdeutlicht und zum anderen durch Kontrastierung mit Daten aus HIC die globale Ungleichheit aufgezeigt werden.

1.4.3. Inzidenz

Die relative Häufigkeit von Krebserkrankungen wird regelhaft in neudiagnostizierten Fällen pro 100.000 Einwohner*innen pro Jahr (n/100.000/a) angegeben, wobei für Vergleiche zwischen verschiedenen Ländern oder über die Zeit hinweg zusätzlich eine Altersstandardisierung gegen verschiedene etablierte, teils abstrakte Standardbevölkerung sinnvoll sein kann.[20]

Für Regionen innerhalb von SSA reichten im Jahr 2018 die altersstandardisierten Inzidenzraten des Zervixkarzinoms von 26,8 im Zentralen Afrika bis 43,1/100.000/a im Südlichen Afrika, wobei die höchste Inzidenzrate aus Simbabwe mit 62,3/100.000/a berichtet wurde. Das bedeutet in absoluten Zahlen, dass von den weltweit geschätzten 570.000 Neudiagnosen im Jahr 2018 112.000 (20 %) auf SSA entfallen, [21] obwohl dort nur 9,4 % der Frauen, die weltweit älter als 20 Jahre sind, leben.[22]

Dieses Missverhältnis erklärt sich durch einen Blick in die USA als HIC: Während dort die Inzidenzrate des Zervixkarzinoms 1935 – vor der Einführung der zytologischen Vorsorgeuntersuchungen – mit über 40/100.000/a altersstandardisiert mit der in SSA heute vergleichbar ist,[23] sank in den USA die altersstandardisierte Inzidenzrate auf 7.4/100.000/a (Jahre 2010-2014).[24]

Die Häufigkeit des Zervixkarzinoms ist aber nicht allein aufschlussreich über die Belastung von Individuum und Gesundheitssystem, sondern das Stadium bei Diagnose hat wesentlichen Einfluss auf den Umfang der notwendigen Therapie.

1.4.4. Stadium bei Diagnose

Die Stadieneinteilung beim Zervixkarzinoms wird weltweit durch die Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) kuratiert, eine Darstellung im etablierten Tumor-Nodalstatus-Metastasen(TNM)-System der Weltorganisation gegen den Krebs (UICC) ist etabliert. Wesentliche Merkmale sind Größe und Infiltrationstiefe des Primärtumors, der Lymphknotenstatus pelvin und paraaortal sowie Vorhandensein von Fernmetastasen. Beachtenswert dabei ist, dass für Therapieentscheidungen wesentliche „Stadiensprünge“ weiterhin auf Befunden basieren, die durch gynäkologische Tastuntersuchungen und einfache Histopathologie erhoben werden können. Während die aktuellste FIGO-Stadieneinteilung von 2019 einige therapierelevante Änderungen im Detail aufweist,[25] ist die Version von 2009,[26] die

im Einschlusszeitraum dieser Arbeit 2010-2016 gültig war, Grundlage dieser Arbeit wie auch einiger relevanter Vergleichspopulationen.

Den besten Aufschluss über das Stadium bei Diagnose geben populationsbezogene Untersuchungen, bei denen in einem Registergebiet mit großem Aufwand alle relevanten Einrichtungen der Krankenversorgung aufgesucht werden und das Stadium anhand von Aktenlage oder aber Telefonanruf und Hausbesuch mit Anamnese und Akteneinsicht so genau wie möglich ermittelt wird. Solche Untersuchungen liegen für SSA nur sehr vereinzelt vor, so in zwei Kohorten aus den 1990er Jahren.[27][28]Abseits von diesen beiden kleineren Kohorten aus den 1990er Jahren existiert eine kürzlich veröffentlichte multinationale populationsbasierte Studie zu Patientinnen aus den Jahren 2005-2015, bei denen 68,5 % der Patientinnen im Stadium III und IV diagnostiziert wurden.[29] Im Vergleich dazu wurden in Deutschland in den Jahren 2017-2018 nur 39 % der Patientinnen im Stadium III und IV diagnostiziert.[3]

Die hohen Stadien bei Diagnose unterstreichen zum einen die anzunehmende große Krankheitslast mit entsprechendem Therapiebedarf und -kosten, zum anderen sind sie eng verbunden mit der Prognose des Überlebens.

1.4.5. Überleben

Man bedient sich der biometrisch leicht fassbaren Überlebensdauer ausgehend von individuellen Ereigniszeit-Daten (time-to-event) ab Diagnose. Da in der populationsbasierten Krebsepidemiologie, insbesondere in SSA, die Todesursache selten verfügbar ist, wird anstatt des krebsspezifischen Überlebens meist das Gesamtüberleben (overall survival: OS) verwendet, was zudem in einigen Ländern wegen fehlender Personenstandsregister per Telefonanruf durch die Krebsregister ermittelt werden muss. Die so ermittelte absolute Sterblichkeit unter den Krebspatient*innen kann zusätzlich um die länderspezifische Grundsterblichkeit in den verschiedenen Altersgruppen einer Kohorte bereinigt werden (relatives Überleben).[30] In einem letzten Schritt kann dieses Gesamtüberleben wie die Inzidenzrate altersadjustiert werden gegen eine spezielle Standardpatient*innenpopulation für die jeweilige Krebsentität.[31] Das Ergebnis ist ein altersstandardisiertes relatives Überleben (ASRS) mit dem Ziel der verbesserten Vergleichbarkeit zwischen Patient*innenpopulationen mit unterschiedlicher Altersstruktur international oder über die Zeit hinweg.

Für das Überleben von Zervixkarzinompatientinnen in SSA stehen wie beim Stadium nur wenige populationsbasierte Daten zur Verfügung, die drei im vorangegangenen Abschnitt vorgestellten Arbeiten entstammen: Das 5-Jahres-ASRS in Uganda lag bei 49

%, das 3-Jahres-ASRS Simbabwe lag bei 45 % in den Jahren 1995-1997.[27][28] Eine aktuelle Studie, die zum Teil auf Beiträgen aus der vorliegenden Arbeit beruht, zeigte über 13 Register in elf Ländern hinweg ein relatives 1-, 3- und 5-Jahres-Überleben von 69,8 %, 44,5 % und 33,1 % in den Jahren 2005 bis 2015,[29] sodass von einem konstant schlechten Überleben in SSA ausgegangen werden kann. Im Vergleich dazu schwankte das relative 5-Jahres-Überleben in den USA von 1990 bis 2013 zwischen 68,8 % und 72,6 % – war also mehr als doppelt so hoch wie in der oben genannten aktuellen Studie in SSA.[32]

Die drei vorgestellten quantitativen epidemiologischen Aspekte von Inzidenz, Stadium bei Diagnose und Überleben lassen den Schluss auf eine relevante Krankheitslast in SSA selbst zu, legen aber auch den Verdacht auf eine globale Ungleichheit nahe.

1.4.6. Erklärungsansätze für Ungleichheit

Für die Ungleichzeit von Inzidenz, Stadium bei Diagnose und Überleben beim Zervixkarzinom zwischen SSA und Ländern mit hohem Einkommen auf der Welt gibt es Erklärungsmöglichkeiten aus verschiedenen Blickwinkeln:

1.4.6.1. Prävention

Wie in *1.3.1 Biologie* ausgeführt, ist die Auftretenswahrscheinlichkeit des Zervixkarzinoms wirkungsvoll beeinflussbar. Die Prävention steht zwar nicht im Fokus dieser Arbeit, aber es sei darauf hingewiesen, dass die in *1.3.3 Inzidenz* dargelegten Erfolge des Systems des engmaschigen zytologischen Screenings wegen der Ressourcenintensität nicht direkt auf SSA übertragbar sein werden. Übersichtsarbeiten und die Strategie der Weltgesundheitsorganisation zur Eliminierung des Zervixkarzinoms „90-70-90 %“ schlagen deshalb basierend auf Evidenzqualität, Machbarkeit und Kosteneffektivität vor: Flächendeckend ist ein integriertes Konzept anzustreben aus mindestens einer HPV-Impfung bei 90 % aller Mädchen im Alter bis 15 Jahre, einem HPV-Test oder vergleichbarem Präzisionstest bei 70 % aller Frauen im Alter von 35 und erneut 45 Jahren sowie adäquater Therapie der präinvasiven und invasiven Karzinome bei 90 % aller Patientinnen.[33][34] Eine relevante Verringerung der Neudiagnosen des invasiven Karzinoms ist ein zentraler Angriffspunkt, um Krankheitslast sowohl von den Patientinnen und ihren Familien als auch den Gesundheitssystemen in SSA zu nehmen. [33] Einer geringeren Anzahl von Patientinnen stünden so auch mehr Diagnose- und Therapiekapazitäten zur Verfügung.

1.4.6.2. Onkologische Diagnostik

Nach der klinischen oder zytologischen Verdachtsdiagnose eines invasiven Zervixkarzinoms ist die histologische Sicherung angezeigt, um seltene

Differentialdiagnosen wie den Müllerschen Mischtumor oder das Sarkom, die einer anderen Therapie bedürften, auszuschließen. Zusätzlich ist für die Stadieneinteilung, Therapieplanung und Prognoseabschätzung die Umfelddiagnostik nötig. In Industriestaaten wird dabei zunehmend auf radiologische und chirurgische Diagnostik gesetzt, vornehmlich mit Ultraschall, Magnetresonanztomografie im Becken und Computertomographie für Abdomen und Thorax sowie diagnostischer bzw. diagnostisch-therapeutischer Lymphonodektomie pelvin und gegebenenfalls paraaortal. Die FIGO-Stadieneinteilung von 2008/2009, die Grundlage dieser Arbeit ist, macht – wie bis vor kurzem folglich auch die meisten klinischen Studien zum Zervixkarzinom – jedoch keinen Unterschied zwischen den Mitteln der Befunderhebung und ermöglicht entsprechend auch die Therapieindikation auf Basis einfacherer Diagnostik im Sinne der klinischen Untersuchung. Allerdings haben Menschen in LMIC nicht immer zuverlässig und zeitgerecht Zugang zu histopathologischer Diagnostik, Röntgen des Thorax, Ultraschall oder gar Computer- oder Magnetresonanztomografie.[35]

1.4.6.3. Onkologische Chirurgie

Die onkologische Chirurgie ist die wesentliche Therapiemodalität in den Stadien I und II, wobei hier ein vereinfachter Überblick über die stadiengerechte Chirurgie gegeben werden soll: Bis zum FIGO-Stadium IA1, also dem minimal-invasiven Karzinom bis 3 Millimeter (mm) Tiefe und 7 mm Breite, verschiedene Arten der Entfernung der Läsion selbst ausreichen können, z.B. die Konisation mittels Schlinge oder Messer. Darüber hinaus wird bei weiterer Ausdehnung (IA2) und insbesondere makroskopisch sichtbaren Läsionen (IB) oder Befall von Uterus und oberem Drittel der Vagina (IIA) die Entfernung des gesamten Uterus mit den Parametrien nötig im Rahmen der radikalen Hysterektomie – regelhaft kombiniert mit einer pelvinen Lymphonodektomie.[14] Die alleinige chirurgische Therapie von Tumoren mit Befall der Parametrien (IIB) oder darüber hinaus mit therapeutischer radikaler Entfernung von lymphatischem Gewebe wird vereinzelt im Rahmen von Studien praktiziert,[36] wurde aber nicht empfohlen in der dieser Arbeit zugrundeliegenden Clinical Practice Guideline 2010 des National Comprehensive Cancer Network (NCCN) aus den USA.[37]

Allerdings ist die qualifizierte onkologische Chirurgie in SSA nicht selbstverständlich verfügbar: Weltweit haben nach Schätzungen einer Lancet Oncology Commission drei Viertel der Patient*innen keinen Zugang zu zeitgerechter und bezahlbarer Krebschirurgie.[38] Dabei seien die Lücken in SSA mit 93 % der Krebspatient*innen ohne Zugang neben Südasien weltweit am größten.[39]

1.4.6.4. Strahlentherapie

Die externe Strahlentherapie wird als weitere wesentliche kurative Therapiemodalität in den Stadien IB, II und III, oft kombiniert mit einer Brachytherapie,[14][40] sowie teils zur palliativen Therapie genutzt. Bei Tumoren in den Stadien IB bis IIA besteht eine teilweise Überlappung der Empfehlungen zur definitiven chirurgischen Versorgung und der primären Strahlentherapie bzw. zur adjuvanten Strahlentherapie – je nach Risikofaktoren einschließlich postoperativem pathologischen Befund, Allgemeinzustand, Alter, Patientinnenwunsch und gegebenenfalls auch Verfügbarkeit: Es gibt Länder in SSA, in denen keine Strahlentherapiegeräte zur Verfügung stehen oder lediglich ältere Geräte, die effektivere und nebenwirkungsärmere Therapieformen wie die intensitätsmodulierte Strahlentherapie nicht unterstützen.[41] Die Internationale Atomenergie-Organisation (IAEA) hat einen umfassenden Überblick über Art und Anzahl der Strahlentherapiegeräte weltweit und hat deren Anzahl den Bevölkerungsgrößen und der Anzahl an Krebspatient*innen gegenübergestellt, die auf sie angewiesen sind. Dabei schätzt sie, dass 50 % der Krebspatient*innen in LMIC und sogar 90 % der Krebspatient*innen in Low-income countries (LIC), zu denen viele Staaten in SSA gehören,[6] keinen Zugang haben.[42]

1.4.6.5. Chemotherapie

Die alleinige Chemotherapie hat in der kurativen Therapie des Zervixkarzinoms keinen Stellenwert. Sie wird jedoch seit Beginn der 2000er Jahre begleitend zur kurativen Strahlentherapie eingesetzt, bei der sie als „Radiosensitizer“ die Effektivität der Bestrahlung verbessert und eine Verbesserung des Überlebens bewirkt.[43] Dabei waren im Erhebungszeitraum dieser Arbeit Cisplatin als Alkylans, gegebenenfalls kombiniert mit 5-Floururacil als Antimetabolit, empfohlen. Faktisch ist aber die Bezahlbarkeit und die Verfügbarkeit in SSA eingeschränkt.[44][45]

Der Nutzen als neoadjuvante Therapie vor Chirurgie – auch gegebenenfalls zum Erreichen eines operativ heilbaren Stadiums – ist umstritten,[46] aber möglicherweise von Interesse, wenn Strahlentherapie nicht verfügbar ist. Für das metastasierte und rezidivierende Zervixkarzinom kann Cisplatin gegebenenfalls ergänzt um Paclitaxel als Spindelgift infrage kommen.[47] Wegen der zum Erhebungszeitpunkt fehlenden Empfehlung für die Neoadjuvanz und der hochindividuellen Therapieentscheidung beim metastasierten Zervixkarzinom sowie der Exklusion von Patientinnen, deren Erstregistration mit Rezidiv erfolgte, wurden diese in der strukturierten Therapiequalitätsbewertung der vorliegenden Arbeit nicht berücksichtigt.

1.5. Zielstellung dieser Arbeit

Aus der Makroperspektive sind in Abschnitt *1.3.6 Erklärungsansätze für Ungleichheit* die wahrscheinlichen Hindernisse für eine adäquate Therapie bei Zervixkarzinompatientinnen in SSA aufgezeigt worden. Der Perspektivwechsel hin zur individuellen Patientin, die je nach sozioökonomischem Status, Herkunftsland, Stadium und Zufall sehr unterschiedlich von diesen Hindernissen betroffen sein könnte, ist bisher selten gemacht worden in der Literatur. So ist dem Autor dieser Arbeit keine bevölkerungsbasierte Studie in SSA bekannt, bei der die Qualität der oft nötigen multimodalen Therapie in Abhängigkeit vom Stadium bewertet worden wäre und sogar eine Assoziation der Therapiequalität mit dem Überleben untersucht worden wäre. Daraus ergaben sich sechs wesentliche Forschungsfragen:

1. Wie ist die Verteilung der FIGO-Stadien bei Diagnose in der eigenen Kohorte und ist sie mit anderen populationsbasierten Untersuchungen aus Subsahara-Afrika vergleichbar?
2. Was bedeutet das Ergebnis der Therapiebewertung in der eigenen Kohorte hochgerechnet für das Schicksal der 120.000 jährlich neu diagnostizierten Zervixkarzinompatientinnen in SSA?
3. Wie ist das Gesamtüberleben in der eigenen Kohorte im geografischen populationsbasierten Vergleich?
4. Ist die Therapiequalität (als Grad der Leitlinientreue) mit unterschiedlichem Gesamtüberleben vergesellschaftet nach Adjustierung für relevante Einflussfaktoren?
5. Wie ist die Leitlinienadhärenz der eigenen Kohorte im internationalen Vergleich mit populationsbasierten Kohorten einzuordnen?
6. Gibt es einen Zusammenhang zwischen Möglichkeit zur externen Strahlentherapie und der Leitlinienadhärenz der Therapie in einem Registergebiet?

2. Diskussion

Im Rahmen des Promotionsprojekts hat der Autor auch zu anderen Krebsentitäten Daten erhoben und an Publikationen mitgewirkt. In dieser Dissertationsschrift werden dabei nur die beiden Publikationen diskutiert, die einen Bezug zum Zervixkarzinom haben. Der Relevanz entsprechend wird zuerst die multinationale Studie zum Zervixkarzinom betrachtet,(Griesel et al., 2021, [48]) auf der auch der Schwerpunkt der Dissertation liegt. Darauf folgt die mononationale Pilotstudie in Äthiopien.(Feuchtner et al., 2019, [49])

2.1. Das Zervixkarzinom in Subsahara-Afrika: Eine multinationale populationsbasierte Kohortenstudie zu Therapiequalität und Überleben

2.1.1. Therapie und ihre Leitlinienadhärenz

Das alarmierendste Ergebnis der Studie war, dass von 632 Patientinnen der populationsbasierten Stichprobe nur 15 % eine Therapie mit kurativem Potential erhielten. Neben weiteren 16 %, die mit FIGO-Stadium IV keiner sinnvollen Bewertung der Therapie auf Leitlinienadhärenz zugänglich waren, konnte bei zwei Drittel der Patientinnen mit Zervixkarzinom trotz gründlicher Datensammlung keine dokumentierte gegen den Krebs gerichtete Therapie unabhängig von kurativem Potential (Chirurgie, Strahlentherapie, Chemotherapie; cancer-directed therapy: CDT) festgestellt werden. Es ist wahrscheinlich, dass bei einem wesentlichen Teil dieser Patientinnen auch tatsächlich keine Therapie erfolgt ist (vgl. *2.2.3. Stärken und Limitationen* der Pilotstudie). Außerdem erhielten von den ausgewählten Patientinnen mit einer Bias-reduzierten Therapiebewertung in der „Therapy association cohort“ (mindestens drei Monate Überleben und Stadium I-III, n=190) nur die Hälfte eine CDT mit kurativem Potenzial, also stadiengerechte Chirurgie oder Strahlentherapie mit Mindestdosis 45 Gray. Es ist also allgemein von relevant unzureichenden Kapazitäten in der gynäkologisch-onkologischen Chirurgie und Strahlentherapie auszugehen. Zwischen den einzelnen Ländern variierte der Anteil der Patientinnen, die eine CDT mit kurativem Potential erhielten, zwischen 49 % in Nairobi (Kenia) und 4 % in Maputo (Mosambik). Die vorliegende Studie wurde hauptsächlich in Hauptstädten durchgeführt (Ausnahmen: Eldoret (Kenia) und Bulawayo (Simbabwe), beides jedoch wichtige Wirtschaftszentren). In allen Registergebieten gab es onkologische Referenzzentren, die jedoch nur teilweise mit Strahlentherapiegeräten ausgestattet waren und die Patientinnen lebten relativ nah bei den Referenzzentren. Gemessen an internationalen Empfehlungen verfügten alle Registergebiete jedoch über viel zu wenige Strahlentherapieeinrichtungen.[50] In dem Zusammenhang konnte festgestellt werden, dass wenn in Registergebieten externe

Strahlentherapie/Teletherapie (EBRT) zur Verfügung stand, eine CDT mit kurativem Potenzial für 15 % bis 49 % der Patientinnen möglich war (Addis Abeba (Äthiopien), Nairobi (Kenia) und Kampala (Uganda)), während nur 10% der Patientinnen in Registergebieten ohne EBRT eine CDT mit kurativem Potenzial erhielten – mit Ausnahme von Eldoret mit 23 %, wo ein Früherkennungs-Programm schon während des Einschlusszeitraums existierte.[51]

Hochgerechnet auf ganz SSA bedeutet die Therapiebewertung, dass nur 28.000 von 112.000 jährlich neu diagnostizierten Zervixkarzinompatientinnen eine CDT mit kurativem Potenzial erhalten würden. 38.000 bis 56.000 würden eine CDT ohne kurativ Potenzial oder keine CDT erhalten und 28.000 Patientinnen würden im FIGO-Stadium IV diagnostiziert und am ehesten eine individuelle palliative Versorgung benötigen.[21] Im Allgemeinen ist beim Zervixkarzinom die unimodale Therapie zunehmend erklärtes Ziel.[14] Jedoch erfordert die Versorgung insbesondere Patientinnen mit FIGO-Stadium ≥II (86,5 % der Patientinnen mit Daten zur Stadieneinteilung in der vorliegenden Studie) oft eine spezialisierte multimodale Therapie qualifizierter onkologischer Chirurgie und Strahlentherapie extern und intern mit konkurrenter Chemotherapie. Angesichts der Daten zu den individuellen Krankengeschichten einschließlich der teils zusätzlich angegebenen Gründe für nicht erfolgte Therapie (v.a. finanzielle Engpässe als Hindernisse für selbstzuzahlende Therapie, lange Wartezeit auf bzw. fehlende Strahlentherapie im Land) kann postuliert werden, dass die Hindernisse, die einer leitliniengerechten Behandlung im Wege standen, sich decken mit den einleitend in *1.3.6. Erklärungsansätze für Ungleichheit* skizzierten.

Veröffentlichungen für den globalen Vergleich sind selten: In einer populationsbasierten australischen Kohorte wurde mit vergleichbarem Maßstab die Behandlung von 54,1 % der Patientinnen im Zeitraum 2005-2011 als leitliniengerecht eingestuft.[52] Das Ergebnis von strikter Leitlinientreue bei nur 30 (16 %) von 190 Patientinnen mit verzerrungsarmer Therapiebewertung (Therapy association cohort) ist damit die mit Abstand niedrigste Rate, die bisher in der Literatur berichtet wurde.

Mit Bezug auf die eingangs erwähnte „90-70-90 %“-Strategie der WHO zur Eliminierung des Zervixkarzinoms muss zusammenfassend festgestellt werden, dass in relevanten Teilen von SSA noch eine deutliche Diskrepanz zwischen dem Ziel von über 90 % adäquater Therapie der Karzinome und der Versorgungsrealtität bestand im Erhebungszeitraum 2010-2016.[53] Mit Blick in die Zukunft sei erwähnt, dass es durchaus Anstrengungen gibt, die Therapiekapazitäten in SSA auszubauen. Beispielhaft

sei das FIDE Global Educational Network der Arbeitsgemeinschaft Frauengesundheit in der Entwicklungszusammenarbeit der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe genannt, das Ausbildungsaufenthalte für internationale gynäkologische Operateur*innen in Deutschland organisiert.[54] Auch gibt es in den Ländern, in denen für diese Studie Daten erhoben wurden, Erfolge und weitere feste Pläne dahingehend, mit großem Aufwand Strahlentherapiekapazitäten auszubauen. Jedoch ist die Anzahl heute tatsächlich schon einsatzbereiter Geräte seit der Datenerhebung faktisch in nur geringem Umfang angestiegen. Dabei liegt die Anzahl der Teletherapiegeräte pro einer Million Einwohner*innen dort weiter deutlich unter 1 (z.B. Benin: 0, Äthiopien: 0,025 oder Kenia: 0,3), während sie in Deutschland über 6 und in den USA über 11 liegt.[54, 55] Bei solch eklatanten Unterschieden muss von einem Problem globaler Ungerechtigkeit in der Ressourcenverteilung ausgegangen werden.

2.1.2. Überleben und Einflussfaktoren

Die Analyse der eigenen Überlebensraten ergab ein 1-, 3- und 5-Jahres-ASRS von 75,6 %, 42,4 % und 28,7 %. Das ist gut vergleichbar mit den 2005-2015 populationsbasiert erhobenen Raten für zusätzliche Länder in SSA mit 69,8 %, 44,5 % und 33,1 %, sowie den 1- und 3-Jahres-ASRS-Schätzungen aus Uganda (81,4 % und 49 %) und Simbabwe (66 % und 44,9 %) aus den Jahren 1995-1997, wobei die Referenzpopulation für die Standardisierung leicht abweicht bei der letzteren.[28][29] Im Gegensatz dazu ist die Schätzung aus dem US-amerikanische Surveillance, Epidemiology, and End Results Program (SEER) von 67,1 % 5-Jahres-ASRS für den Zeitraum 2007-2013 als Beispiel für die Überlebensrate in einem HIC wesentlich höher. Wie zu erwarten war, hatten Patientinnen in den FIGO-Stadien I und II eine deutlich bessere Überlebenswahrscheinlichkeit als Patientinnen in den FIGO-Stadien III und IV. Angesichts dessen ist anzustreben, dass die Karzinome und ihre Vorstufen bestenfalls in einem Screeningprogramm mit Präzisionstest früh entdeckt werden und für eine schnelle Überweisung gesorgt wird. Die WHO empfiehlt in ihrer Strategie „90-70-90 %“, dass 70 % der Frauen sich dazu zweimal im mittleren Lebensalter mindestens einem molekularbiologischem HPV-Test oder ähnlich sensitivem und spezifischen Verfahren unterziehen, also nicht der teils in SSA noch gängigen makroskopischen Inspektion nach Essigsäureanwendung.[53]

Der Zusammenhang der Leitlinientreue mit dem Überleben wurde zur Bias-Minimierung nur bei der Gruppe mit bekannten FIGO-Stadien I-III und ≥3 Monaten Beobachtungszeit (n=190) und adjustiert für bekannte prognostische Faktoren analysiert. Dabei war für die Leitlinienadhärenz quasi ein Dosis-Wirkungs-Effekt auf der Ordinalskala zu beobachten, wobei die Hazard-Rate-Ratio für frühen Tod mit geringerer Leitlinientreue zunahm. Eine

Behandlung mit kleineren Abweichungen von der Leitlinie war mit einem 1,7-mal erhöhten Risiko für frühen Tod, größere Abweichungen waren mit einem doppelt so hohen Risiko verbunden. "CDT ohne kurativ Potenzial" und "keine CDT" waren im Vergleich zu einer leitliniengerechten Behandlung mit einem vierfach bzw. sogar neunfach höheren Risiko verbunden.

Nach Beginn der Datenerhebung und Therapiebewertung der vorliegenden Arbeit im Jahr 2017 erstellte das NCCN „harmonisierte“ Leitlinien für ressourcenlimitierte Regionen wie SSA.[47] Diese Leitlinien enthalten Empfehlungen zur Standardbehandlung, aber auch zu Alternativen, falls ausreichende Ressourcen nicht zur Verfügung stehen. Der Effekt der Umsetzung dieser harmonisierten NCCN-Leitlinien für SSA kann aus ethischen Gründen nicht in einer randomisierten Studie untersucht werden. Der in der vorliegenden Studie beobachtete Zusammenhang zwischen unterschiedlichem Grad der Therapietreue und besserem Überleben unterstützt die Grundsätze dieser Leitlinien, die bei Bedarf spezifische Abweichungen von der Optimalversorgung nahelegen, die das Bewertungsschema der vorliegenden Studie teils ebenfalls vorsieht. Da zeitnah nur schrittweise und kleinere Verbesserungen in der flächendeckenden Versorgung des Zervixkarzinoms in SSA zu erwarten sind, erscheint also die Anwendung der „harmonisierten“ Leitlinien weiterhin empfehlenswert. Heilversuche jedoch, die im Bereich von „CDT ohne kurativ Potential“ im Bewertungsschema der vorliegenden Arbeit geführt sind, sollten nicht unternommen werden, da sie mit einem fast vierfachen Risiko des frühen Todes im Vergleich zur leitliniengerechten Therapie assoziiert waren. Gleichzeitig verursachen sie wahrscheinlich trotzdem eine erhebliche Morbidität und finanzielle Belastung für Patientinnen und Familienangehörige.[56] Natürlich ist es ebenfalls nicht akzeptabel, wenn Patientinnen in einer kurativen Situation ohne CDT behandelt werden, da das assoziierte Risiko eines frühen Todes um das Neunfache erhöht ist.

Für den Vergleich mit einem HIC anhand oben eingeführter australischer Kohorte wurde eigens eine abgewandelte Regression modelliert: Bei Patientinnen im FIGO-Stadium I und II mit vollständig leitliniengerechter Behandlung war das Risiko eines frühen Todes in der vorliegenden Studie (HRR, 0,30; KI 0,11-0,86; n = 111) ähnlich der entsprechenden australischen Subkohorte (HRR, 0,22; KI 0,07-0,75; n = 106) relevant verringert.[52] Eine leitlinienadhärente Therapie im Vergleich zu einer Therapie ohne Leitlinienadhärenz erscheint folglich sowohl in SSA als auch in HIC möglicherweise lohnenswert – unter Einbezug der methodischen Limitation.

2.1.3. Stärken und Limitationen

Wesentliche Limitationen dieser Arbeit sind teils mangelhafte Dokumentation von Stadium und Therapie sowie ein frühzeitiges Ende der Nachbeobachtung, was die Regel auch in vergleichbaren Studien in SSA ist.[27][28][45][57] Es ist davon auszugehen, dass die erreichte Vollständigkeit den Umständen entsprechend mit adäquatem Aufwand nicht zu verbessern ist. Außerdem handelt es sich um eine retrospektive Kohorte, die wegen vieler bekannter und anzunehmender unbekannter Einflussfaktoren per se nicht dazu geeignet ist, eine direkte Kausalität von nur beobachteten Zusammenhängen abzuleiten.

Darüber hinaus ist davon auszugehen, dass die Regressionsanalysen in dieser retrospektiven Untersuchung im Sinne eines Survival-Bias dadurch verzerrt wurden, dass bei Diagnose bzw. Einschluss noch offen war, ob und welche Art von Therapie eine Patientin erhalten würde: Es konnte also ein, das eine Patientinnen mit fortgeschrittener Erkrankung und frühem Tod (Endpunkt) unter Umständen keine Chance hatten, eine Therapie (Exposition) zu beginnen und somit zu einem niedrigeren Überleben in der Gruppe ohne Therapie beigetragen haben könnten. Ebenso war analog von einem Bias zugunsten der Patientinnen durch so genannte „Immortal time“ auszugehen, die als Patientinnen mit Behandlung gewertet wurden – das heißt, sie mussten mindestens bis zum Ende einer unter Umständen aufwändigen Therapie überlebt haben, sonst wären sie in eine Gruppe mit schlechterer Therapiebewertung eingeordnet worden. In einer retrospektiven Studie ist diese Bias-Art nicht grundsätzlich zu vermeiden und mit einer für den Zeitpunkt der Exposition – in diesem Fall der Therapie – adjustierenden zeitabhängigen Cox-Regression kann prinzipiell eine Korrektur versucht werden. Das war allerdings wegen zu oft fehlenden Datumsangaben kritischer Therapieschritte nicht möglich. Deshalb wurde entschieden, in die Regressionsanalyse nur Patientinnen mit einer mindestens dreimonatigen Überlebenszeit bzw. Beobachtungszeit nach Diagnose einzubeziehen im Sinne einer „Landmark-Analyse“. Auch damit konnte der wahrscheinlich aus dieser Bias-Art folgenden „Überblähung“ des Therapieeffekts ein Stück weit begegnet werden [58].

Dass Patientinnen eine angezeigte Therapie beginnen und sogar abschließen konnten, geschah möglicherweise nicht zufällig, sondern wurde auch von Faktoren beeinflusst, die mit dem Überleben assoziiert gewesen sein könnten, für die jedoch nicht adjustiert wurde. Dabei sind vor allem Komorbiditäten zu erwähnen, die zum Zeitpunkt der Diagnose noch keinen Einfluss auf den Allgemeinzustand hatten (in der Cox-Regression als Grad der Einschränkungen bei Aktivitäten des täglichen Lebens anhand der Eastern-Cooperative-Oncology-Group(ECOG)-Klassifikation repräsentiert). Diese konnten sich

aber später verschlimmert haben oder eine Kontraindikation für Therapien gewesen sein könnten, wie eine Niereninsuffizienz für die konkurrente Chemotherapie.

Die vorgelegten Ergebnisse sind darüber hinaus auch deswegen als tendenziell optimistisch einzustufen, weil die Daten von Einwohnerinnen von Großstädten und ihrer Umgebung stammen und nur fraglich auf die Bevölkerung in ländlichen Regionen verallgemeinerbar sind, da dort der Zugang zur Therapie noch eingeschränkter sein dürfte.

Auf der anderen Seite ist eine wesentliche Stärke dieser Arbeit, dass Patientinnen durch Stichproben aus bevölkerungsbasierten Registern ausgewählt wurden, bei denen es im Gegensatz zu deutlich leichter durchführbaren krankenhausbasierten Studien keinen Selektionsbias gibt. Die Ergebnisse zu den Stadien, der Anzahl der unbehandelten Patientinnen, den 1- und 3-Jahres-Überlebensraten und dem Anteil der bekannt HIV-positiven Patientinnen ähnelten denen vergleichbarer Studien aus Uganda, Simbabwe und Äthiopien und einer multinationalen Studie aus SSA, was eine akzeptable Repräsentativität der eigenen Kohorte annehmen lässt.[27][28][29][45] Die Tatsache, dass insgesamt 22 der 410 erfolgreich nachverfolgten Patientinnen innerhalb des ersten Monats verstarben (unter diesen medianes Überleben: sieben Tage), zeigt, dass die späte Vorstellung und die späte formale Diagnose ein weiterer Grund für die sehr kurzen Überlebenszeiten in der untersuchten Kohorte sind. So kann für die Überlebenszeiten in der vorliegendenden Arbeit in der Abwesenheit von flächendeckendem Screening von einem geringen Lead-time-Bias ausgegangen werden. Das wiederum bedeutet bezüglich vergleichend herangezogenen Daten aus den USA, wo Patientinnen vorrangig in früheren Stadien diagnostiziert werden, dass eventuell nicht die gesamte Diskrepanz bei den Überlebenszeiten der höheren Therapiequalität dort zuordenbar ist.

2.2. Die häufigsten Krebsentitäten und ihre Therapie in Addis Abeba (Äthiopien)

2.2.1. Charakteristika

Die häufigsten fünf Krebsarten bei 588 Patient*innen in Addis Abeba waren Mammakarzinom (28,1 %), Zervixkarzinom (8,7 %), Karzinom an Kolon und Rektum (7,7 %), Non-Hodgkin-Lymphom (6,8 %) und Bronchialkarzinom (4,6 %). Die Patient*innen waren meist unter 60 Jahre alt, was in Zusammenschau mit der Altersstruktur Äthiopiens plausibel erscheint. [59] Ein großer Anteil (38,8 %) aller Krebspatient*innen befand sich bei Diagnose schon im Stadium IV, was konsistent ist mit den einführend in Abschnitt *1.3.4 Stadium bei Diagnose* dargestellten Daten für das Zervixkarzinom in SSA und einer äthiopischen Kohortenstudie aus 2010-2016 bei Mammakarzinompatientinnen, also den beiden häufigsten Entitäten der Population in Addis Abeba.[60]

2.2.2. Therapie

Es erhielten rund 50 % der dafür infrage kommenden Patient*innen ihre geplante Chemotherapie binnen sechs Monaten nach Diagnose und etwa 25 % die geplante Strahlentherapie binnen sechs Monaten. 50 % der Patient*innen wurden wegen ihres Primärtumors operiert.

Von 188 Patient*innen, bei denen eine Strahlentherapie angezeigt war, erhielten 46 (25 %) die geplante Dosis, eine sehr kleine Gruppe von 4 Patientinnen (2 %) erhielt weniger als 85% der verschriebenen Dosis, während 45 (24 %) ihre geplante Strahlentherapie nie begannen und bei 73 (39 %) nie eine Strahlentherapie geplant wurde. Außerdem betrug die mediane Wartezeit auf eine Strahlentherapie 6,9 Monate. Diese Ergebnisse sind bedauerlich, da es speziell für das Zervixkarzinom aus Äthiopien starke Hinweise gibt, dass während der langen Wartezeit eine Erhöhung des Tumorstadiums häufig ist.[45] Jedoch passen die Ergebnisse zu den in *1.3.6.4. Strahlentherapie* vorgestellten Lücken der Strahlentherapiekapazitäten in LMIC. Dies gilt insbesondere für Äthiopien, wo es während des Einschlusszeitraumes der vorliegenden Studie nur ein einziges Cobalt-60-Teletherapiegerät gab für rund 110.000.000 Einwohner*innen.

2.2.3. Stärken und Limitationen

In Populationen mit einem so eingeschränkten Zugang zu modernen onkologischen Therapiemodalitäten ist das populationsbasierte Studiendesign essenziell, um Informationen auch zu möglichst all denjenigen Patient*innen sammeln zu können, die nur punktuelle Kontakte mit dem schulmedizinischen Gesundheitssystem hatten und womöglich über die klinische Diagnose hinaus keine Leistung erhalten haben. Es konnten die Akten zu etwa der Hälfte der eingeschlossenen Patient*innen gefunden

werden. Es muss davon ausgegangen werden, dass bei den meisten anderen Patient*innen tatsächlich keine onkologische Therapie stattgefunden hat, weil Therapieakten in der Regel in den Einrichtungen verbleiben. Auch war es nicht möglich, aus der Retrospektive individuelle Therapieansätze für Patient*innen im Stadium IV zu bewerten und nur in Ausnahmefällen ausdrückliche Begründungen für das Abweichen von Therapieplänen zu eruieren.

2.2.4. Konsequenzen dieser Vorarbeit

Neben dem eigenen großen Wert der Studie in Addis Abeba diente sie auch als Pilotstudie für die Machbarkeit der multinationalen populationsbasierten Studie zu Krebstherapie und Überleben in SSA. Der festgestellte zeitliche und finanzielle Aufwand der Nachverfolgung beeinflusste wesentlich die Zeit- und Personalplanung sowie die Stichprobengrößen in den einzelnen Registern. Ebenso fiel auf Basis von Inzidenzraten in ganz SSA, aber auch den in Addis Abeba erhobenen Stadien und ihrer kurativen Therapierbarkeit die Wahl auf die fünf Entitäten Mammakarzinom, Karzinom von Kolon und Rektum, Non-Hodgkin-Lymphom, Prostatakarzinom und Zervixkarzinom. Weiterhin wurden die Variablen der Datensammlung zu Charakteristika und Therapie auf ihre Praktikabilität und sinnvolle retrospektive Erhebbarkeit überprüft und angepasst. Auch die Arbeitsteilung und Verantwortlichkeiten der deutschen Doktorand*innen, der afrikanischen Registermitarbeiter*innen und der Koordinationsbüros in Halle (Saale) und Oxford während der Datensammlungsphase wurde auf Basis der Arbeit in Addis Abeba festgelegt. Nicht zuletzt flossen Daten aus der Vorarbeit als vollwertiger Beitrag Äthiopiens in die multinationale Studie ein.

3. Literaturverzeichnis

1. Medizinische Fakultät Halle (Saale). Empfehlung zur geschlechtersensiblen Sprache, 2022. Available at: https://www.umh.de/fileadmin/Dokumente/Dokumente/Prodekanat_Genderfragen/Empfehlung_Geschlechtersensible_Sprache_Glossar_27062022.pdf Accessed November 08, 2023.

2. Kruk ME, Gage AD, Arsenault C et al. High-quality health systems in the Sustainable Development Goals era: time for a revolution. The Lancet Global Health 2018;6(11):e1196-e1252.

3. Robert-Koch-Institut. Krebs in Deutschland für 2017/2018. Berlin, 2021.

4. Crocker-Buque T, Pollock AM. Appraising the quality of sub-Saharan African cancer registration systems that contributed to GLOBOCAN 2008: A review of the literature and critical appraisal. Journal of the Royal Society of Medicine 2015;108(2):57–67.

5. www.afcrn.org Accessed December 29, 2018.

6. World Bank. World Bank Country and Lending Groups by 2020. Available at: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups Accessed January 18, 2022.

7. Centers for Disease Control and Prevention. Mortality in the United States, 2020, 2022. Available at: https://www.cdc.gov/nchs/products/databriefs/db427.htm.

8. Statista. Sub-Saharan Africa: Life expectancy at birth from 2009 to 2019. Available at: https://www.statista.com/statistics/805644/life-expectancy-at-birth-in-sub-saharan-africa/ Accessed January 21, 2022.

9. Gouda HN, Charlson F, Sorsdahl K et al. Burden of non-communicable diseases in sub-Saharan Africa, 1990–2017: results from the Global Burden of Disease Study 2017. The Lancet Global Health 2019;7(10):e1375-e1387.

10. Ferlay J, Shin H-R, Bray F et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International Journal of Cancer 2010;127(12):2893–2917.

11. Parkin DM, Ferlay J, Jemal A, Borok M, Manraj SS, N'da GG, Ogunbiyi FJ, Liu B, Bray F, ed. Cancer in Sub-Saharan Africa.

12. International Agency For Research On Cancer. GLOBOCAN 2020: Sub-Saharan Africa Hub. Available at: https://gco.iarc.fr/today/data/factsheets/populations/971-sub-saharan-africa-hub-fact-sheets.pdf Accessed January 21, 2022.

13. zur Hausen H. Papillomaviruses in the causation of human cancers. Virology 2009;2009:260–265.

14. Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF (Leitlinienprogramm Onkologie). S3-Leitlinie Diagnostik, Therapie und Nachsorge der Patientin mit Zervixkarzinom: Langversion, 2021.

15. Jaquet A, Odutola M, Ekouevi DK et al. Cancer and HIV infection in referral hospitals from four West African countries. Cancer Epidemiology 2015;39(6):1060–1065.

16. Ginsburg O, Bray F, Coleman MP et al. The global burden of women?: S cancers: a grand challenge in global health. The Lancet 2017;389(10071):847–860.

17. Lagomarsino G, Garabrant A, Adyas A et al. Moving towards universal health coverage: Health insurance reforms in nine developing countries in Africa and Asia. The Lancet 2012;380(9845):933–943.

18. Arrossi S, Matos E, Zengarini N et al. The socio-economic impact of cervical cancer on patients and their families in Argentina, and its influence on radiotherapy compliance. Results from a cross-sectional study. Gynecologic oncology 2007;105(2):335–340.

19. Soerjomataram I, Lortet-Tieulent J, Parkin DM et al. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. The Lancet 2012;380(9856):1840–1850.

20. National Cancer Institute. Standard Populations (Millions) for Age-Adjustment. Available at: https://seer.cancer.gov/stdpopulations/ Accessed June 17, 2023.

21. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians 2018;68(6):394–424.

22. United Nations, Department of Economic and Social Affairs, Population Divison (2017). World Population Prospects: The 2017 Revision, custom data acquired via website. Available at: https://population.un.org/wpp/Publications/ Accessed February 18, 2019.

23. Devesa SS SDT. Cancer Incidence and Mortality Trends in the United States: 1935-74. Journal of the National Cancer Institute 1978;60(3):545–571.

24. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA. SEER Cancer Statistics Review, 1975-2014. Available at: https://seer.cancer.gov/csr/1975_2014/ Accessed February 04, 2018.

25. Bhatla N, Berek JS, Cuello Fredes M et al. Revised FIGO staging for carcinoma of the cervix uteri. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2019;145(1):129–135.

26. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. International Journal of Gynecology & Obstetrics 2009;105(2):103–104.

27. Wabinga H, Ramanakumar AV, Banura C et al. Survival of cervix cancer patients in Kampala, Uganda: 1995-1997. British Journal of Cancer 2003;89(1):65–69.

28. Chokunonga E, Ramanakumar AV, Nyakabau AM et al. Survival of cervix cancer patients in Harare, Zimbabwe, 1995-1997. International Journal of Cancer 2004;109(2):274–277.

29. Sengayi-Muchengeti M, Joko-Fru WY, Miranda-Filho A et al. Cervical cancer survival in sub-Saharan Africa by age, stage at diagnosis and Human Development Index: A population-based registry study. International Journal of Cancer 2020;147(11):3037–3048.

30. Hakulinen TR, Dyba TA. Recent Developments in Relative Survival Analysis. In: Outcome Prediction in Cancer: Elsevier, 2007:43–64.

31. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. European Journal of Cancer 2004;40(15):2307–2316.

32. National Cancer Institute. SEER Cancer Statistics Review 1975-2014 Survival: Table 5.8: Cancer of the Uterine Cervix (Invasive). Available at: https://seer.cancer.gov/archive/csr/1975_2014/browse_csr.php?sectionSEL=5&pageSEL=sect_05_table.08 Accessed January 18, 2022.

33. Sankaranarayanan R, Anorlu RI, Sangwa-Lugoma G et al. Infrastructure requirements for human papillomavirus vaccination and cervical cancer screening in sub-Saharan Africa. Vaccine 2013;31 Suppl 5:F47-52.

34. Denny L, Sanjose S de, Mutebi M et al. Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries. The Lancet 2017;389(10071):861–870.

35. Wilson ML, Atun R, DeStigter K et al. The Lancet Commission on diagnostics: advancing equitable access to diagnostics. The Lancet 2019;393(10185):2018–2020.

36. Höckel M, Wolf B, Schmidt K et al. Surgical resection based on ontogenetic cancer field theory for cervical cancer: mature results from a single-centre, prospective, observational, cohort study. The Lancet Oncology 2019;20(9):1316–1326.

37. Greer BE et al. Practice Guidelines in Oncology: Cervical Cancer V. 1.2010: The National Comprehensive Cancer Network NCCN; https://de.scribd.com/document/369113825/Cervical, accessed 11.11.2023. Alternativ bei Aktualisierung: https://drive.google.com/file/d/12FFCfYM5xvkFANQUWJgDBUGmXFC5ftXe/view?usp=sharing, 2009 und beim Autor.

38. Sullivan R, Alatise OI, Anderson BO et al. Global cancer surgery: Delivering safe, affordable, and timely cancer surgery. The Lancet Oncology 2015;16(11):1193–1224.

39. Meara JG, Leather AJM, Hagander L et al. Global Surgery 2030: Evidence and solutions for achieving health, welfare, and economic development. The Lancet 2015;386(9993):569–624.

40. Han K, Milosevic M, Fyles A et al. Trends in the utilization of brachytherapy in cervical cancer in the United States. International Journal of Radiation Oncology, Biology, Physics 2013;87(1):111–119.

41. https://dirac.iaea.org/Data/CountriesLight Accessed December 06, 2020.

42. Zubizarreta E, van Dyk J, Lievens Y. Analysis of Global Radiotherapy Needs and Costs by Geographic Region and Income Level. Clinical oncology (Royal College of Radiologists (Great Britain)) 2017;29(2):84–92.

43. Vale CL, et al. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: A systematic review and meta-analysis of individual patient data from 18 randomized trials. Journal of clinical oncology official journal of the American Society of Clinical Oncology 2008;26(35):5802–5812.

44. Yohana E, Kamuhabwa A, Mujinja P. Availability and affordability of anticancer medicines at the Ocean Road Cancer Institute in Dar es Salaam, Tanzania. East African Journal of Public Health 2011;8(1):52–57.

45. Kantelhardt EJ, Moelle U, Begoihn M et al. Cervical cancer in Ethiopia: Survival of 1,059 patients who received oncologic therapy. The Oncologist 2014;19(7):727–734.

46. Rydzewska L, Tierney JF, Vale CL et al. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. The Cochrane database of systematic reviews 2012;12:CD007406.

47. Koh WJ et al. NCCN Harmonized Guidelines for Sub-Saharan Africa: Cervical Cancer 1.2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cervical_harmonized-africa.pdf accessed 31.08.2018. alternativ bei Aktualisierung: https://drive.google.com/file/d/13L8VkaadvQY56jjzX_IiIdEKprEmnCo-/view?usp=sharing und beim Autor.

48. Griesel M, Seraphin TP, Mezger NCS et al. Cervical Cancer in Sub-Saharan Africa: A Multinational Population-Based Cohort Study of Care and Guideline Adherence. The Oncologist 2021;26(5):e807-e816.

49. Feuchtner J, Mathewos A, Solomon A et al. Addis Ababa population-based pattern of cancer therapy, Ethiopia. PloS one 2019;14(9):e0219519.

50. Abdel-Wahab M, Bourque JM, Pynda et al. Status of radiotherapy resources in Africa: an International Atomic Energy Agency analysis. The Lancet Oncology 2013(4):e168-75.

51. Were E, Nyaberi Z, Buziba N. Perceptions of risk and barriers to cervical cancer screening at Moi Teaching and Referral Hospital (MTRH), Eldoret, Kenya. African Health Sciences 2011;11(1):58–64.

52. Chiew K-L, Chong S, Duggan KJ et al. Assessing guideline adherence and patient outcomes in cervical cancer. Asia-Pacific Journal of Clinical Oncology 2017;13(5):e373-e380.

53. World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem. Genf, 2020.

54. AG FIDE e.V. FGEN – FIDE Global Educational Network. Available at: https://ag-fide.org/fgen/ Accessed August 23, 2023.

55. International Atomic Energy Agency. Number of Radiotherapy Machines Per Million People. Available at: https://dirac.iaea.org/Query/Map2?mapId=0 Accessed August 23, 2023.

56. Moelle U, Mathewos A, Aynalem A et al. Cervical Cancer in Ethiopia: The Effect of Adherence to Radiotherapy on Survival. The Oncologist 2018.

57. Allemani C, Matsuda T, Di Carlo V et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): Analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. The Lancet 2018.

58. Suissa S. Immortal time bias in pharmaco-epidemiology. American Journal of Epidemiology 2008;167(4):492–499.

59. Ethiopia—Life expectancy at birth 2016. Available at: https://countryeconomy.com/demography/life-expectancy/ethiopia Accessed January 19, 2022.

60. Eber-Schulz P, Tariku W, Reibold C et al. Survival of breast cancer patients in rural Ethiopia. Breast cancer research and treatment 2018;170(1):111–118.

4. Thesen

1. In der retrospektiven multinationalen Krebsregisterstudie in acht Ländern Subsahara-Afrikas (SSA) befanden sich die Tumoren zum Diagnosezeitpunkt bei mindestens 61 % der Patientinnen im FIGO-Stadium III und IV. Der Anteil der fortgeschrittenen Stadien lag deutlich über dem deutschen von 39 %. Die späte Diagnose am ehesten durch fehlende Vorsorgeuntersuchungen zeigt weltweite Ungleichheit.

2. In der Stadien-abhängigen Therapiebewertung lag die Leitlinientreue bei nur 16 %. Das ist die mit Abstand niedrigste Rate, die bisher in der internationalen Literatur berichtet wurde.

3. Die vergleichbar gemachten Gesamtüberlebensraten lagen für fünf Jahre bei 28,7 % in meiner Untersuchung versus 67,1 % in den Vereinigten Staaten von Amerika. Untermauert durch die Punkte 1 und 2 halte ich es für plausibel, dass die Sterblichkeit des Zervixkarzinoms weltweit verhinderbar unterschiedlich ist.

4. Der Therapiebedarf steht in einem immensen Missverhältnis zu den vorhandenen Ressourcen insbesondere im Bereich der Strahlentherapie und wird in absehbarer Zeit nicht gedeckt werden können. Der wirkungsvollen und auch in SSA praktisch machbaren Prävention des Zervixkarzinoms sollte daher in Zukunft Priorität eingeräumt werden.

5. Definierte Abweichungen der Therapie von der Leitlinie waren mit teils gering, teils deutlich erhöhtem Risiko für frühen Tod vergesellschaftet. Es kann mit Vorsicht gefolgert werden, dass bei begrenzten Ressourcen Therapien mit kleineren Abweichungen vertretbar sind. Solche, die kein kurativ Potential bieten, aber mit erheblichen Nebenwirkungen einhergehen können, kamen häufig vor, sollten jedoch dringend vermieden werden.

5. Publikationsteil

Diese Arbeit ist Teil der „Therapy and Outcome Study“ als gemeinsames Projekt der Martin-Luther-Universität Halle-Wittenberg, dem Afrikanischem Krebsregisternetzwerk und den einzelnen Registern. Dabei war ich der erste von fünf Doktorand*innen, der nach der Pilotphase (Addis Abeba) mit Kolleg*innen vor Ort Datenerhebung durchführte und im Anschluss mit der Datenanalyse begann. Daten zu fünf Krebsentitäten wurden in allen Registern in gemeinsamer Datenbank gesammelt und dann für jede Entität ausgewertet. Für die vorgelegte Dissertation mit Fokus Zervixkarzinom sind meine Erstautorenschaft (1.) und die mitverfasste Pilotstudie (2.) von vorrangiger Bedeutung.

Im Einzelnen bestand die eigene Leistung aus:

Studienkonzeption; Datenerhebung; Koordination in drei von elf beteiligten Krebsregistern (Bulawayo (Simbabwe), Eldoret (Kenia) und Nairobi (Kenia)) von Oktober 2016 bis April 2017; Datenanalyse einschließlich Therapiebewertungsschema; statistische Analyse; federführendes Erstellen des Manuskripts und der Abbildungen; Kongressvorträge:

1. **Griesel, Mirko**; Seraphin, Tobias P.; Mezger, Nikolaus C. S.; Hämmerl, Lucia; Feuchtner, Jana; Joko-Fru, Walburga Yvonne; Sengayi-Muchengeti, Mazvita; Liu, Biying; Vuma, Samukeliso; Korir, Anne; Chesumbai, Gladys C.; Nambooze, Sarah; Lorenzoni, Cesaltina F.; Akele-Akpo, Marie-Thérèse; Ayemou, Amalado; Traoré, Cheick B.; Wondemagegnehu, Tigeneh; Wienke, Andreas; Thomssen, Christoph; Parkin, Donald M.; Jemal, Ahmedin; Kantelhardt, Eva J. (2021): Cervical Cancer in Sub-Saharan Africa: A Multinational Population-Based Cohort Study of Care and Guideline Adherence. In: The Oncologist. DOI: 10.1002/onco.13718

Mitarbeit bei Datenanalyse und Erstellen des Manuskripts der Pilotstudie; Ableitung von Konsequenzen für das sich anschließende Gesamtprojekt zu fünf Krebsarten bei:

2. Feuchtner, Jana; Mathewos, Assefa; Solomon, Asmare; Timotewos, Genebo; Aynalem, Abreha; Wondemagegnehu, Tigeneh; Gebremedhin, Amha; Adugna, Fekadu; **Griesel, Mirko** et al. (2019): Addis Ababa population-based pattern of cancer therapy, Ethiopia. In: PLoS ONE. DOI: 10.1371/journal.pone.0219519

Studienkonzeption; Datenerhebung in drei von elf beteiligten Krebsregistern (Bulawayo (Simbabwe), Eldoret (Kenia) und Nairobi (Kenia)) von Oktober 2016 bis April 2017; Mitarbeit bei Datenanalyse und Erstellen des Manuskripts bei:

3. Seraphin, Tobias, Joko-Fru, Walburga Hämmerl, Lucia, **Griesel, Mirko** et al. (2021): Presentation, patterns of care, and outcomes of patients with prostate cancer in sub-Saharan Africa: A population-based registry study. In: Cancer. DOI: 10.1002/cncr.33818.

4. Mezger, Nikolaus C. S.; Feuchtner, Jana; **Griesel, Mirko** et al. (2020): Clinical presentation and diagnosis of adult patients with non-Hodgkin lymphoma in Sub-Saharan Africa. In: British Journal of Haematology. DOI: 10.1111/bjh.16575.

5. Mezger, Nikolaus Christian Simon; Hämmerl, Lucia; **Griesel, Mirko** et al. (2023): Guideline Concordance of Treatment and Outcomes Among Adult Non-Hodgkin Lymphoma Patients in Sub-Saharan Africa: A Multinational, Population-Based Cohort. In: The Oncologist. DOI: 10.1093/oncolo/oyad157

6. Joko-Fru, Walburga Yvonne; **Griesel, Mirko** et al. (2021): Breast Cancer Diagnostics, Therapy, and Outcomes in Sub-Saharan Africa: A Population-Based Registry Study. In: Journal of the National Comprehensive Cancer Network: JNCCN. DOI: 10.6004/jnccn.2021.7011.

6. Erklärungen

1. Ich erkläre, dass ich mich an keiner anderen Hochschule einem Promotionsverfahren unterzogen bzw. eine Promotion begonnen habe.

2. Ich erkläre, die Angaben wahrheitsgemäß gemacht und die wissenschaftliche Arbeit an keiner anderen wissenschaftlichen Einrichtung zur Erlangung eines akademischen Grades eingereicht zu haben.

3. Ich erkläre an Eides statt, dass ich die Arbeit selbstständig und ohne fremde Hilfe verfasst habe. Alle Regeln der guten wissenschaftlichen Praxis wurden eingehalten; es wurden keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt und die den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht.

Leipzig, den 15.09.2024	Mirko Griesel

7. Danksagung

Mein besonderer Dank gilt meiner Doktormutter Prof.in Eva Kantelhardt, die alle Schritte des Projekts einschließlich der herausfordernden Datensammlung im Ausland mit großem Engagement begleitet hat. Neben der medizinischen und akademischen Begleitung ist sie mit ihrem Idealismus und dem Streben nach internationaler Zusammenarbeit auf Augenhöhe auch menschlich immer eine Quelle der Inspiration für mich gewesen.

Ebenso gilt mein Dank und meine Anerkennung allen Kolleg*innen in den beteiligten regionalen Krebsregistern, die oft unter prekären finanziellen Umständen und mit großem Idealismus an der Datensammlung für das Projekt mitgewirkt und abseits davon über Jahre die notwendigen Strukturen aufgebaut haben. Besonders erwähnt seien hierbei Ann Kosgei, Gladys Chesumbai und Prof. Nathan Buziba aus Eldoret (Kenia), Nathan Okerosi und Dr.in Anne Korir aus Nairobi (Kenia) sowie Prof.in Samukeliso Vuma aus Bulawayo (Simbabwe) für ihre Unterstützung und Gastfreundschaft bei meinen mehrmonatigen Einsätzen in ihren Krebsregistern.

Weiterhin danke ich Biying Liu und Prof. Donald Maxwell Parkin für die Koordination und Unterstützung bei der Datensammlung sowie für ihre unermüdliche Arbeit für das Afrikanische Krebsregisternetzwerk.

Prof. Rafael Mikolajczyk und Prof. Andreas Wienke sowie allen anderen Mitarbeiter*innen des Instituts für Medizinische Epidemiologie, Biometrie und Statistik an der Medizinischen Fakultät der Martin-Luther-Universität Halle-Wittenberg danke ich für die Möglichkeit, mich an ihrem Institut promovieren lassen zu dürfen sowie für die infrastrukturelle und inhaltliche Unterstützung bei meinem Projekt und den Publikationen. Die allgemeine biostatistische Ausbildung, die ich in Arbeitsgruppensitzungen und Kursen am Institut als externer Doktorand erfahren habe, schätze ich sehr.

Meinen Mitdoktorand*innen Dr.in Jana Feuchtner, Lucia Hämmerl, Nikolaus Mezger, Dr. Tobias Seraphin und Dr.in Yvonne Walburga Joko-Fru danke ich für die freundschaftliche und fruchtvolle Zusammenarbeit bei der Datensammlung und den gemeinsamen Publikationen, das gegenseitige Vertrauen und die intensiven gemeinsamen Erfahrungen.

Meinem Bruder, meinem Vater und meiner zwischenzeitlich verstorbenen Mutter danke ich herzlich für stete Ermutigung und Unterstützung. Dieser Dank gilt ebenso meinen Freund*innen und Weggefährt*innen.

Ich bedanke mich bei der Friedrich-Ebert-Stiftung e.V. für die finanzielle Unterstützung bei der Datensammlung zum Projekt sowie für die finanzielle und ideelle Förderung während des gesamten Studiums, die mich zusammen mit der Förderung durch meine Familie in die privilegierte Position gebracht haben, ein so umfangreiches Promotionsprojekt in Angriff nehmen zu können.

The Oncologist®

Global Health and Cancer

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

Mirko Griesel,[a] Tobias P. Seraphin,[a] Nikolaus C.S. Mezger,[a] Lucia Hämmerl,[a] Jana Feuchtner,[a] Walburga Yvonne Joko-Fru,[c,d] Mazvita Sengayi-Muchengeti,[e] Biying Liu,[d] Samukeliso Vuma,[f] Anne Korir,[g] Gladys C. Chesumbai,[h] Sarah Nambooze,[i] Cesaltina F. Lorenzoni,[j] Marie-Thérèse Akele-Akpo,[k] Amalado Ayemou,[l] Cheick B. Traoré,[m] Tigeneh Wondemagegnehu,[n] Andreas Wienke,[a] Christoph Thomssen,[b] Donald M. Parkin,[c,d] Ahmedin Jemal,[o] Eva J. Kantelhardt[a,b]

[a]Institute of Medical Epidemiology, Biostatistics, and Informatics and [b]Department of Gynaecology, Martin-Luther-University, Halle-Wittenberg, Germany; [c]Clinical Trials Service Unit & Epidemiological Studies Unit, Department of Medicine, University of Oxford, United Kingdom; [d]African Cancer Registry Network, Oxford, United Kingdom; [e]National Cancer Registry, National Health Laboratory Service, South Africa; [f]Department of Radiotherapy, Mpilo Hospital, Bulawayo, Zimbabwe; [g]National Cancer Registry, Kenya Medical Research Institute, Nairobi, Kenya; [h]Eldoret Cancer Registry, Moi Teaching and Referral Hospital, Eldoret, Kenya; [i]Kampala Cancer Registry, Department of Pathology, Makerere University, Kampala, Uganda; [j]Departamento de Patologia, Faculdade de Medicina Universidade Eduardo Mondlane, Maputo, Mozambique; [k]Département D'anatomo-Pathologie, Faculté des Sciences de la Santé, Cotonou, Benin; [l]Oncologie-Radiothérapie, Programme National de Lutte contre le Cancer, Abidjan, Côte d'Ivoire; [m]Service du Laboratoire d'Anatomie et Cytologie Pathologiques C.H.U. du point G, Bamako, Mali; [n]Radiotherapy Center, Addis Ababa University, Ethiopia; [o]Surveillance and Health Services Research, American Cancer Society, Atlanta, Georgia, USA

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

Correspondence: Eva Johanna Kantelhardt, P.D., D.Med., Institute of Medical Epidemiology, Biostatistics and Informatics, Martin Luther University Halle-Wittenberg, Magdeburgerstrasse 8, D-06097 Halle, Germany. Telephone: +49-345-557-4166; e-mail: eva.kantelhardt@uk-halle.de. Received July 10, 2020; accepted for publication January 15, 2021; published Online First on March 10, 2021. http://dx.doi.org/10.1002/onco.13718

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

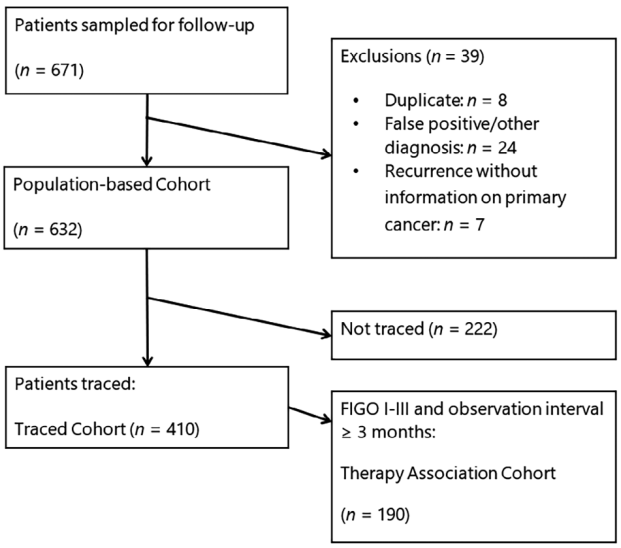


Figure 1. Trial flow diagram. Patients with hospital files found or successful telephone contact were considered to be traced.
Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

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 ≥3 months, FIGO stage ≤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.

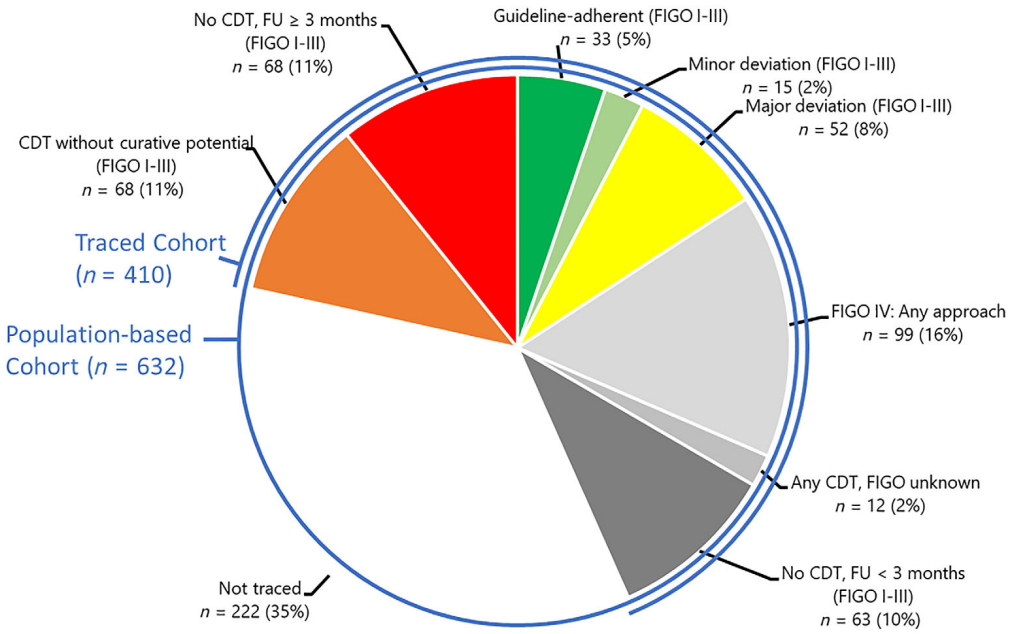


Figure 2. Therapy evaluation in the population-based cohort (*n* = 632). Evaluations refer to the therapy evaluation scheme in Table 1. Colors depict the degree of adherence: green indicates optimal, light green minor deviation, yellow major deviation, orange CDT without curative potential, and red no 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).

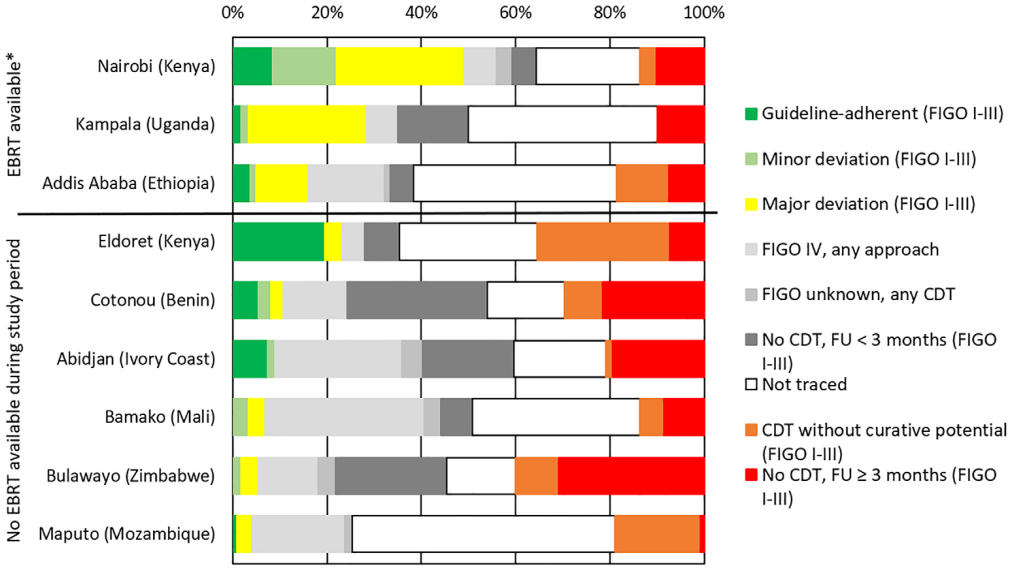


Figure 3. Therapy evaluation in the population-based cohort (*n* = 632) stratified by registry. Evaluations refer to the therapy evaluation scheme in Table 1. Colors depict the degree of adherence: green indicates optimal, light green minor deviation, yellow major deviation, orange CDT without curative 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).

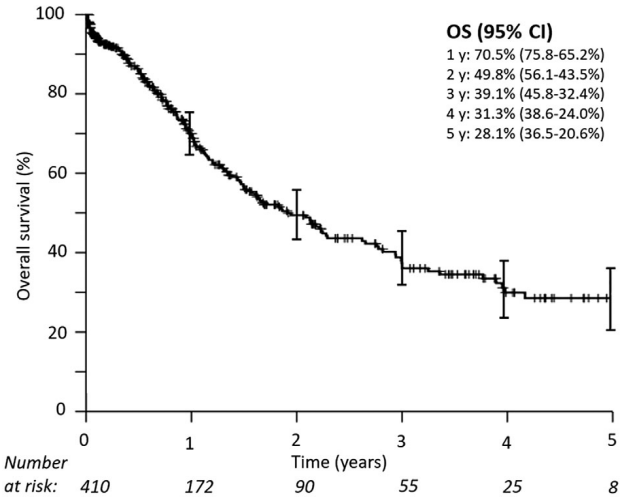


Figure 4. Overall survival in the traced cohort ($n = 410$). Median overall survival was 23 months. Patients with hospital files found or successful telephone contact were considered to be traced.
Abbreviations: CI, confidence interval; OS, overall survival.

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

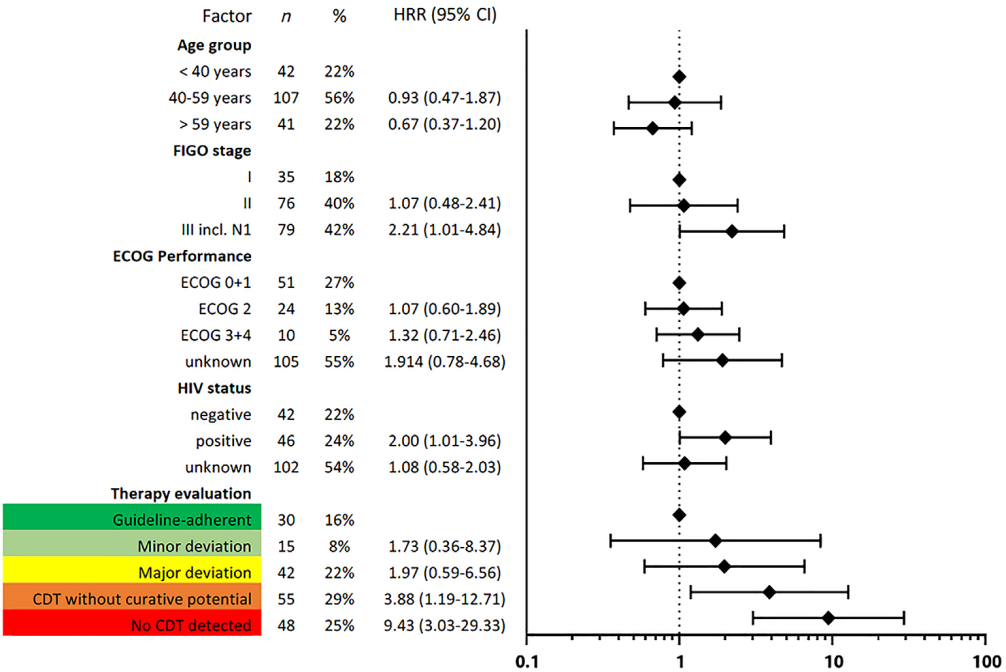


Figure 5. Results of multiple Cox regression for risk of early death in the therapy association cohort ($n = 190$) are shown: through inclusion criteria (FIGO stages I–III and follow-up ≥3 months), bias was reduced. Therapy evaluation refers to Table 1.
Abbreviations: CDT, cancer-directed therapy; CI, 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].

Acknowledgments

We would like to thank all registry staff involved in data collection and follow-up. We were supported by Intramural Funding from the Research Department of the American Cancer Society (contract no. 43359) and the German Ministry for Economic and Development Cooperation (BMZ) through the ESTHER University and Hospital Partnership Initiative of German International Cooperation (GIZ) (project no. 13.2238.7-004.41). The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. Open Access funding enabled and organized by Projekt DEAL.

Author Contributions

Conception/design: Mirko Griesel, Eva J. Kantelhardt

Provision of study material or patients: Samukeliso Vuma, Anne Korir, Gladys C. Chesumbai, Sarah Nambooze, Cesaltina F. Lorenzoni, Marie-Thérèse Akele-Akpo, Amalado Ayemou, Cheick B. Traoré, Tigeneh Wondemagegnehu

Collection and/or assembly of data: Mirko Griesel, Tobias P. Seraphin, Nikolaus C.S. Mezger, Lucia Hämmerl, Jana Feuchtner, Biying Liu

Data analysis and interpretation: Mirko Griesel, Walburga Yvonne Joko-Fru, Andreas Wienke, Christoph Thomssen, Eva J. Kantelhardt

Manuscript writing: Mirko Griesel, Mazvita Sengayi-Muchengeti, Donald M. Parkin, Ahmedin Jemal, Eva J. Kantelhardt

Final approval of manuscript: Mirko Griesel, Tobias P. Seraphin, Nikolaus C.S. Mezger, Lucia Hämmerl, Jana Feuchtner, Walburga Yvonne Joko-Fru, Mazvita Sengayi-Muchengeti, Biying Liu, Samukeliso Vuma, Anne Korir, Gladys C. Chesumbai, Sarah Nambooze, Cesaltina F. Lorenzoni, Marie-Thérèse Akele-Akpo, Amalado Ayemou, Cheick B. Traoré, Tigeneh Wondemagegnehu, Andreas Wienke, Christoph Thomssen, Donald M. Parkin, Ahmedin Jemal, Eva J. Kantelhardt

Disclosures

Eva J. Kantelhardt: Daiichi Sankyo (other: travel support); **Jana Feuchtner:** Bayer Foundation (other: stipend/travel); **Mirko Griesel:** Friedrich Ebert Foundation (other: stipend/travel). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

1. Bach PB. Using practice guidelines to assess cancer care quality. J Clin Oncol 2005;23:9041–9043.

2. Kruk ME, Gage AD, Arsenault C et al. High-quality health systems in the Sustainable Development Goals era: Time for a revolution. Lancet Glob Health 2018;6:e1196–e1252.

3. Devesa SS, Silverman DT. Cancer incidence and mortality trends in the United States: 1935-74. J Natl Cancer Inst 1978;60:545–571.

4. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

5. United Nations, Department of Economic and Social Affairs, Population Divison (2017). World Population Prospects: The 2017 Revision, custom data acquired via website. Available at: https://population.un.org/wpp/Publications/. Accessed February 18, 2019.

6. Wabinga H, Ramanakumar AV, Banura C et al. Survival of cervix cancer patients in Kampala, Uganda: 1995-1997. Br J Cancer 2003;89:65–69.

7. Chokunonga E, Ramanakumar AV, Nyakabau AM et al. Survival of cervix cancer patients in Harare, Zimbabwe, 1995-1997. Int J Cancer 2004;109:274–277.

8. Kantelhardt EJ, Moelle U, Begoihn M et al. Cervical cancer in Ethiopia: Survival of 1,059 patients who received oncologic therapy. ***The Oncologist*** 2014;19:727–734.

9. Sengayi-Muchengeti M, Joko-Fru WY, Miranda-Filho A et al. Cervical cancer survival in sub-Saharan Africa by age, stage at diagnosis and Human Development Index: A population-based registry study. Int J Cancer 2020;147:3037–3048.

10. Abdel-Wahab M, Zubizarreta E, Polo A et al. Improving quality and access to radiation therapy: An IAEA perspective. Semin Radiat Oncol 2017;27:109–117.

11. Meara JG, Leather AJM, Hagander L et al. Global Surgery 2030: Evidence and solutions for achieving health, welfare, and economic development. Lancet 2015;386:569–624.

12. Wilson BE, Jacob S, Yap ML et al. Estimates of global chemotherapy demands and corresponding physician workforce requirements for 2018 and 2040: A population-based study. Lancet Oncol 2019;20:769–780.

13. African Cancer Registry Network Web site. Available at http://afcrn.org/. Accessed December 29, 2018.

14. Finesse AM, Somdyala N, Chokunonga E, Parkin DM. Standard Procedure Manual for Population-Based Cancer Registries in sub-Saharan Africa. Version II, 2015. Available at: http://afcrn.org/resources/51-afcrndatabase/131-sop. Accessed July 31, 2017.

15. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynecol Obstet 2009;105:103–104.

16. National Comprehensive Cancer Network. Practice Guidelines in Oncology: Cervical Cancer. Version 1.2010. Plymouth Meeting, PA: National Comprehensive Cancer Network, 2009.

17. Kerr S, Jazieh AR, Kerr D. How useful are international treatment guidelines in low- and middle-income countries? J Glob Oncol 2017;3: 441–443.

18. Ismaila N, Salako O, Mutiu J et al. Oncology guidelines usage in a low- and middle-income country. J Glob Oncol 2018;4:1–6.

19. Brenner H, Gefeller O, Hakulinen T et al. period and periodh: Period Analysis of Survival Data, 2018. Available at: http://www.imbe.med.uni-erlangen.de/cms/software_period.html. Accessed January 2, 2019.

20. World Health Organization. Global Health Observatory Data Repository: Life tables by country. Available at: http://apps.who.int/gho/data/node.main.LIFECOUNTRY?lang=en. Accessed December 4, 2018.

21. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. Eur J Cancer 2004;40:2307–2316.

22. Chiew KL, Chong S, Duggan KJ et al. Assessing guideline adherence and patient outcomes in cervical cancer. Asia Pac J Clin Oncol 2017;13:e373–e380.

23. Abdel-Wahab M, Bourque JM, Pynda et al. Status of radiotherapy resources in Africa: An International Atomic Energy Agency analysis. Lancet Oncol 2013:e168–e175.

24. Were E, Nyaberi Z, Buziba N. Perceptions of risk and barriers to cervical cancer screening at Moi Teaching and Referral Hospital (MTRH), Eldoret, Kenya. Afr Health Sci 2011;11:58–64.

25. Wilson ML, Atun R, DeStigter K et al. The Lancet Commission on diagnostics: Advancing equitable access to diagnostics. Lancet 2019;393: 2018–2020.

26. Han K, Milosevic M, Fyles A et al. Trends in the utilization of brachytherapy in cervical cancer in the United States. Int J Radiat Oncol Biol Phys 2013;87:111–119.

27. Howlader N, Noone AM, Krapcho M et al. SEER Cancer Statistics Review, 1975-2014. Available at: https://seer.cancer.gov/csr/1975_2014/. Accessed February 4, 2018.

28. National Comprehensive Cancer Network. NCCN Harmonized Guidelines for Sub-Saharan Africa: Cervical Cancer. Plymouth Meeting, PA: National Comprehensive Cancer Network, 2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cervical_harmonized-africa.pdf.

29. Moelle U, Mathewos A, Aynalem A et al. Cervical cancer in Ethiopia: The effect of adherence to radiotherapy on survival. ***The Oncologist*** 2018;23:1024–1032.

30. Allemani C, Matsuda T, Di Carlo V et al.; CONCORD Working Group. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): Analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 2018;391:1023–1075.

31. Suissa S. Immortal time bias in pharmacoepidemiology. Am J Epidemiol 2008;167:492–499.

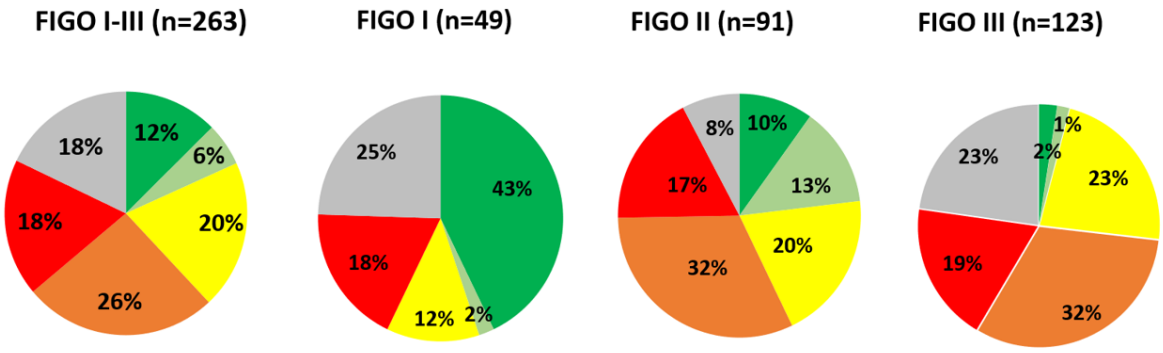
32. Dereje N, Addissie A, Worku A et al. Extent and predictors of delays in diagnosis of cervical cancer in Addis Ababa, Ethiopia: A population-based prospective study. J Glob Oncol 2020;6: 277–284.

33. Höckel M, Wolf B, Schmidt K, et al. Surgical resection based on ontogenetic cancer field theory for cervical cancer: mature results from a single-centre, prospective, observational, cohort study. Lancet Oncol 2019;20(9):1316–1326.

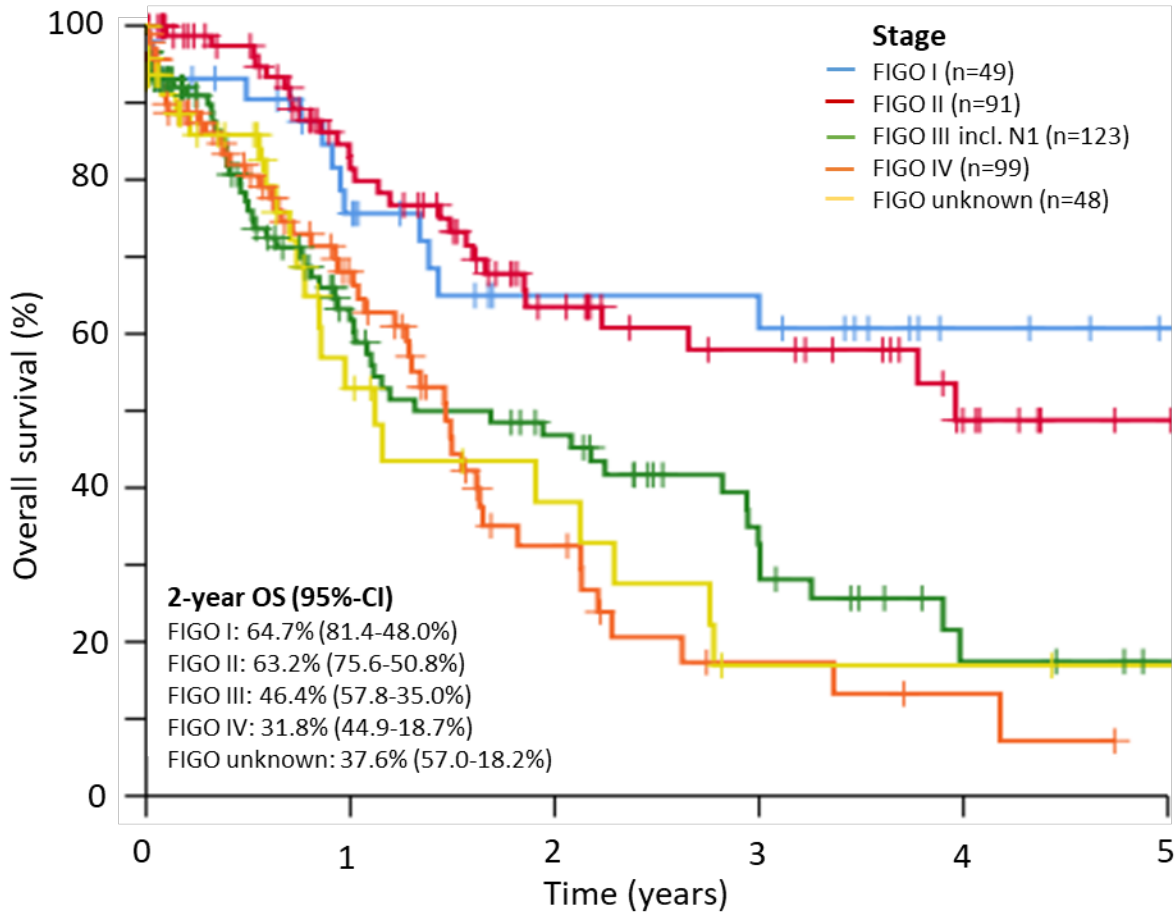
See http://www.TheOncologist.com for supplemental material available online.

The Oncologist
The official journal of the Society for Translational Oncology

Supplemental Figures for:
Cervical cancer in Sub-Saharan Africa: a multinational population-based cohort study on patterns and guideline adherence of care
Eva J Kantelhardt et al.



Supplemental figure 1: Guideline adherence stratified by FIGO stages I-III decreased with increasing stage ($p<0.001$). Colours depict the degree of adherence in green=optimal, light green=minor and yellow=major deviation, orange=CDT without curative potential, red=no CDT and follow-up $\geq$ 3 months, and light grey=no CDT and follow-up < 3 months.



Supplemental figure 2: Overall survival stratified by FIGO stage in “Traced Cohort” (n=410). FIGO I and II vs. III and IV in Log rank test: $p<0.001$. Patients with hospital files found or successful telephone contact were considered as “traced”.

The Oncologist
The official journal of the Society for Translational Oncology

Supplemental Tables for:
Cervical cancer in Sub-Saharan Africa: a multinational population-based cohort study on patterns and guideline adherence of care
Eva J Kantelhardt et al.

Supplemental table 1: The evaluation scheme in the manuscript groups the assumed relative impact of procedures and regimens; not all definitions could be based on controlled trials. Here we present background information on our considerations.

Treatment Modality	Authors	Year	Source	Stage	Comment	Effect	Consequence
Surgery							
Overview	Verleye et al	2009	☐1	FIGO I-IIB	Different types of hysterectomies as of 2009, freely accessible review		Basis of the definition of deviations in primarily surgical patients
Radical surgery in locally advanced disease	Greer et al	2009	☐2	FIGO IIB	Radical hysterectomy is not directly recommended but was under examination in 2009 together with NACT.		Considered minor deviation if combined with lymphadenectomy
Neoadjuvant chemotherapy (NACT)	Greer et al	2009	☐2	FIGO IIB	NACT was under examination in 2009, thus not considered for evaluation.		Not considered
Radiotherapy							
Additional Brachytherapy (BT)	Greer et al Han et al	2009 2013	☐3	FIGO IB-III	If there is intact primary tumour, BT is required and has a strong positive influence on survival.	HRR=0.66	Lack of BT considered major deviation
Concurrent chemotherapy (CT)	Vale et al	2008	☐4	FIGO IB-III	Any curative radiotherapy should be combined with CT, but influence on survival is weaker than BT.	HRR=0.81	Lack of concurrent CT considered minor deviation
Dose of concurrent CT	Eifel et al	2006	☐5	FIGO IB-III	To allow for different established protocols and adaption to patient status and toxicity		Minimum of 2 cycles considered as CT received
Minimum dose of BT for guideline adherence	Greer et al Viswanathan et al Einck et al	2009 2012 2014	2, 6, 7		Guideline recommendation regarding BT is imprecise. Retrospective calculation of bioequivalent dose impossible when documentation was incomplete. Therefore simplification: Any dose equivalent to or higher than established regimens accepted as adequate.		BT doses of ≥16.6 Gy in addition to guideline-recommended 45 Gy external beam radiotherapy
Minimum dose for curative potential	Koh et al	2017	8	FIGO IB-III	Lowest dose recommendation to be found for external beam radiotherapy only is 40 Gy plus “boost”.		45 Gy considered minimum curative dose and major deviation

References of Supplemental table 1

1. Verleye L, Vergote I, Reed N, Ottevanger PB. Quality assurance for radical hysterectomy for cervical cancer: The view of the European Organization for Research and Treatment of Cancer--Gynecological Cancer Group (EORTC-GCG). Ann Oncol 2009; 20(10):1631–8.

2. Greer BE et al. Practice Guidelines in Oncology: Cervical Cancer V. 1.2010; 2009 [cited 2018 Mar 31]. Available from: URL: https://de.scribd.com/document/369113825/Cervical.

3. Han K, Milosevic M, Fyles A, Pintilie M, Viswanathan AN. Trends in the utilization of brachytherapy in cervical cancer in the United States. Int J Radiat Oncol Biol Phys 2013 [cited 2017 Nov 13]; 87(1):111–9.

4. Vale CL, et al. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: A systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol 2008 [cited 2017 Nov 29]; 26(35):5802–12.

5. Eifel PJ. Concurrent chemotherapy and radiation therapy as the standard of care for cervical cancer. Nat Clin Pract Oncol 2006 [cited 2017 Nov 14]; 3(5):248–55.

6. Viswanathan AN, Creutzberg CL, Craighead P, McCormack M, Toita T, Narayan K et al. International brachytherapy practice patterns: a survey of the Gynecologic Cancer Intergroup (GCIG). Int J Radiat Oncol Biol Phys 2012; 82(1):250–5.

7. Einck JP, Hudson A, Shulman AC, Yashar CM, Dieng MM, Diagne M et al. Implementation of a high-dose-rate brachytherapy program for carcinoma of the cervix in Senegal: a pragmatic model for the developing world. Int J Radiat Oncol Biol Phys 2014; 89(3):462–7.

8. Koh WJ et al. NCCN Harmonized Guidelines for Sub-Saharan Africa: Cervical Cancer 1.2017 [cited 2018 Mar 31]. Available from: URL: https://www.nccn.org/professionals/physician_gls/pdf/cervical_harmonized-africa.pdf.

Supplemental table 2: Baseline mortality according to country from WHO life tables; nMx = age-specific death rate between ages x and x+n (http://apps.who.int/gho/data/node.main.LIFECOUNTRY?lang=en (accessed Apr 12, 2018))

Indicator	Age Group	Benin 2013 Female	Ethiopia 2013 Female	Ivory Coast 2013 Female	Mali 2013 Female	Mozambique 2013 Female	Kenya 2013 Female	Uganda 2013 Female	Zimbabwe 2013 Female	Mean of age-specific death rate between ages x and x+n
nMx	<1 year	0.067	0.04	0.065	0.075	0.059	0.035	0.038	0.045	0.0530
nMx	1-4 years	0.01	0.005	0.007	0.013	0.006	0.004	0.005	0.007	0.0071
nMx	5-9 years	0.003	0.002	0.008	0.004	0.004	0.002	0.003	0.002	0.0035
nMx	10-14 years	0.002	0.002	0.004	0.003	0.003	0.002	0.002	0.002	0.0025
nMx	15-19 years	0.002	0.002	0.005	0.003	0.003	0.002	0.002	0.002	0.0026
nMx	20-24 years	0.003	0.002	0.006	0.004	0.005	0.003	0.003	0.003	0.0036
nMx	25-29 years	0.004	0.003	0.007	0.004	0.008	0.003	0.005	0.005	0.0049
nMx	30-34 years	0.004	0.004	0.009	0.005	0.01	0.004	0.006	0.007	0.0061
nMx	35-39 years	0.005	0.005	0.012	0.006	0.013	0.005	0.008	0.013	0.0084
nMx	40-44 years	0.006	0.006	0.013	0.007	0.013	0.006	0.009	0.016	0.0095
nMx	45-49 years	0.007	0.007	0.014	0.008	0.012	0.006	0.011	0.016	0.0101
nMx	50-54 years	0.009	0.008	0.016	0.011	0.013	0.008	0.012	0.016	0.0116
nMx	55-59 years	0.012	0.011	0.02	0.014	0.016	0.011	0.014	0.016	0.0143
nMx	60-64 years	0.019	0.017	0.03	0.022	0.022	0.017	0.019	0.019	0.0206
nMx	65-69 years	0.03	0.027	0.046	0.036	0.033	0.027	0.029	0.028	0.0320
nMx	70-74 years	0.049	0.045	0.072	0.061	0.052	0.044	0.047	0.044	0.0518
nMx	75-79 years	0.079	0.073	0.111	0.102	0.083	0.072	0.076	0.071	0.0834
nMx	80-84 years	0.127	0.12	0.173	0.172	0.132	0.119	0.123	0.115	0.1351
nMx	85+ years	0.224	0.217	0.276	0.285	0.228	0.234	0.22	0.212	0.2370

Supplemental table 3: Therapy receipt and evaluation of degree of guideline adherence (see table 1) in the "Population-based Cohort" stratified by FIGO stage (n=632). Colors depict the degree of adherence: green=optimal, light green=minor and yellow=major deviation, orange=CDT without curative potential, and red=no CDT.

EBRT=External beam radiotherapy, CDT=Cancer-directed therapy, FU=Follow-up, time of observation since diagnosis

Therapy reported in files (regardless of guideline adherence)	"Population-based Cohort" (n=632)	FIGO I (n=49)	FIGO II (n=91)	FIGO III (n=123)	FIGO IV (n=99)	FIGO unknown (n=48
Some form of surgery	82 (13%)	27 (55%)	22 (24%)	17 (14%)	10 (10%)	6 (13%)
Some form of EBRT after surgery	22 (3%)	2 (4%)	9 (10%)	5 (4%)	5 (5%)	1 (2%)
Some form of primary EBRT	73 (12%)	1 (2%)	27 (30%)	32 (26%)	10 (10%)	3 (6%)
Chemotherapy only	66 (10%)	0 (0%)	19 (21%)	23 (19%)	21 (21%)	3 (6%)
No CDT detected at any timepoint	189 (30%)	21 (43%)	23 (25%)	51 (41%)	58 (59%)	36 (75%)
Not traced	222 (35%)					
Therapy evaluation (degree of guideline adherence according to table 1)						
Guideline-adherent	33 (5%)	21 (53%)	9 (12%)	3 (3%)		
Minor deviation	12 (2%)	1 (3%)	12 (16%)	2 (2%)		
Major deviation	52 (8%)	6 (15%)	18 (24%)	28 (28%)		
CDT without curative potential	68 (11%)	0 (0%)	29 (39%)	39 (39%)		
No CDT detected, FU ≥ 3	48 (8%)	12 (30%)	7 (9%)	28 (28%)		
Evaluation not feasible	194 (31%)					
FIGO I-III: No CDT, FU < 3 months	47 (7%)					
FIGO unknown, any therapy or none	45 (7%)					
FIGO IV, any approach	99 (16%)					
Not traced	222 (35%)					

Supplemental table 4: Epidemiological, economical, and cancer care infrastructure indicators. Estimates are the most recent available in the respective international institutions' data tools.

BT=Brachytherapy; EBRT=External beam radiotherapy; GDP=Gross Domestic Product; USD=United States Dollar

Country	Annual cancer cases/inhabitants 2020[1]	Share of GDP spent on health care 2017[2]	GDP per capita as International USD 2019[3]	EBRT machines (MV/MeV therapy) 2019[4]	BT machines 2019[4]	Cancer Centers with radiotelether apy 2020[1]
Benin	5,100/11,176,000	2.49%	3,423.6	0	0	0
Ethiopia	60,960104,957,000	3.30%	2,311.7	2	1	1
Ivory Coast	12,000/24,295,000	4.19%	5,455.4	2	0	1
Kenya	41,000/49,700,000	5.17%	4,509.3	12	5	6
Mali	9,350/18,542,000	3.88%	2,423.8	1	0	1
Mozambique	22,010/29,669,000	8.17%	1,333.5	1	0	1
Uganda	29,380/42,863,000	6.53%	2,271.6	1	1	1
Zimbabwe	15,520/16,530,000	4.73%	2,953.5	7	3	3
USA	1,604,000/324,459,000	16.89%	65,118.4	3536	776	2,153
Australia	122,000/24,451,000	9.28%	53,320.3	218	12	98

REFERENCES

1. https://dirac.iaea.org/Query/Map2?mapId=0 Accessed December 06, 2020.

2. https://data.worldbank.org/indicator/SH.XPD.CHEX.GD.ZS Accessed December 20, 2020.

3. https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD Accessed December 06, 2020.

4. https://dirac.iaea.org/Data/CountriesLight Accessed December 06, 2020.

PLOS ONE

RESEARCH ARTICLE

Addis Ababa population-based pattern of cancer therapy, Ethiopia

Jana Feuchtner[1], Assefa Mathewos[2], Asmare Solomon[2], Genebo Timotewos[2], Abreha Aynalem[2], Tigeneh Wondemagegnehu[2], Amha Gebremedhin[3], Fekadu Adugna[2], Mirko Griesel[1], Andreas Wienke[1], Adamu Addissie[4], Ahmedin Jemal[5], Eva Johanna Kantelhardt[1,6]*

1 Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University Halle-Wittenberg, Halle, Germany, **2** Radiotherapy Center, Addis Ababa University, Addis Ababa, Ethiopia, **3** Division of Hematology, Department of Internal Medicine, Addis Ababa University, Addis Ababa, Ethiopia, **4** School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia, **5** Surveillance and Health Service Reseach, American Cancer Society, Atlanta, Georgia, United States of America, **6** Department of Gynaecology, Medical Faculty, Martin-Luther-University Halle-Wittenberg, Halle, Germany

* eva.kantelhardt@uk-halle.de

Citation: Feuchtner J, Mathewos A, Solomon A, Timotewos G, Aynalem A, Wondemagegnehu T, et al. (2019) Addis Ababa population-based pattern of cancer therapy, Ethiopia. PLoS ONE 14(9): e0219519. https://doi.org/10.1371/journal.pone.0219519

Editor: Erin Bowles, Kaiser Permanente Washington Health Research Institute, UNITED STATES

Received: March 17, 2019

Accepted: August 28, 2019

Published: September 19, 2019

Data Availability Statement: All relevant data are within the manuscript and Supporting Information files.

Funding: The research leading to these results has received funding from the German Ministry of Education and Research under grant agreement n° 01DG12006; the German Ministry for Economic and Development Cooperation (BMZ) through the ESTHER University and Hospital Partnership Initiative of German International Cooperation

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.

(GIZ); the Surveillance and Health Service Research Program, American Cancer Society and the World Health Organization country office. FJ received a doctoral fellowship by the Bayer Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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].

https://doi.org/10.1371/journal.pone.0219519.t001

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.

https://doi.org/10.1371/journal.pone.0219519.t002

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

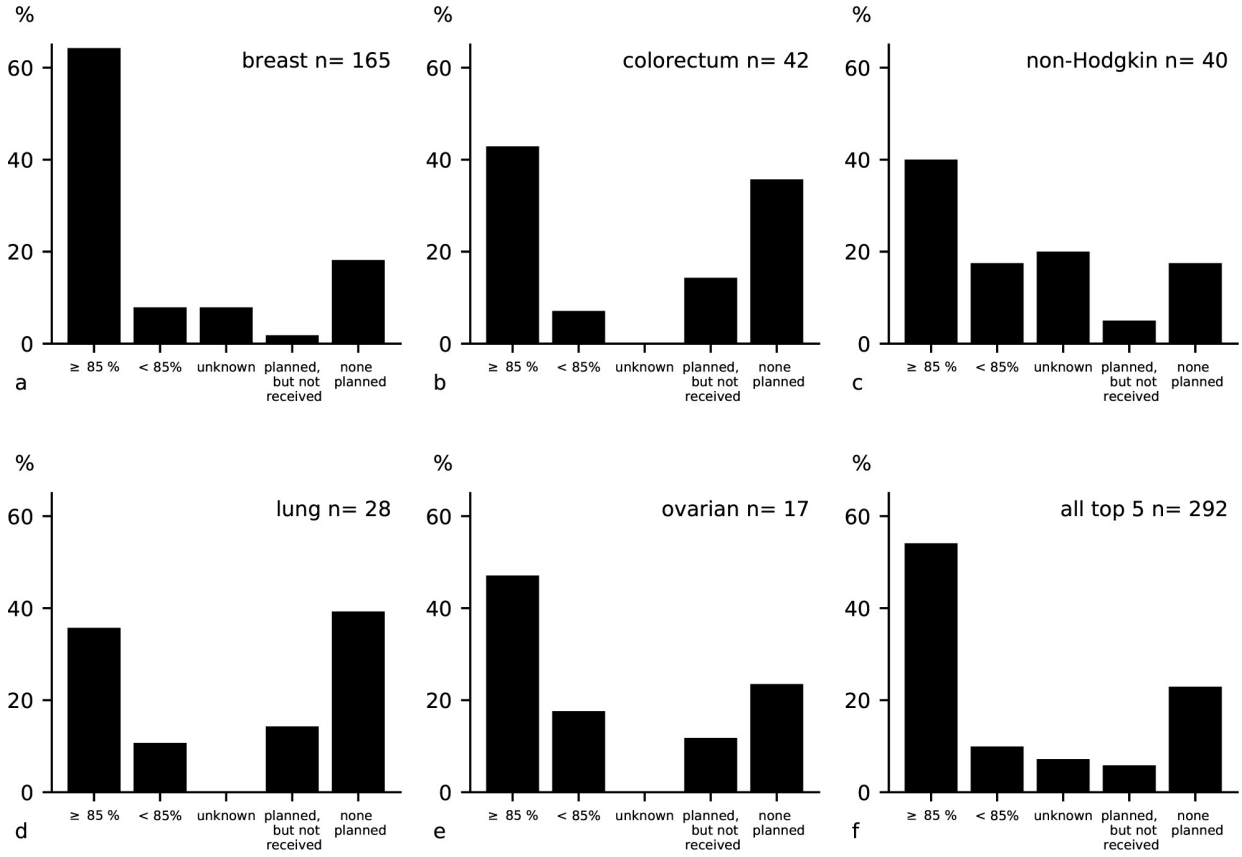


Fig 1. Completeness of chemotherapy according to local guidelines in top 5 cancer entities: (a) breast cancer stages 1–4; (b) colorectal cancer stages 3–4; (c) Non-Hodgkin's lymphoma stages 2–4; (d) lung cancer stages 2–4; (e) ovarian cancer stages 2–4; (f) all 5 cancer entities together.

https://doi.org/10.1371/journal.pone.0219519.g001

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%)

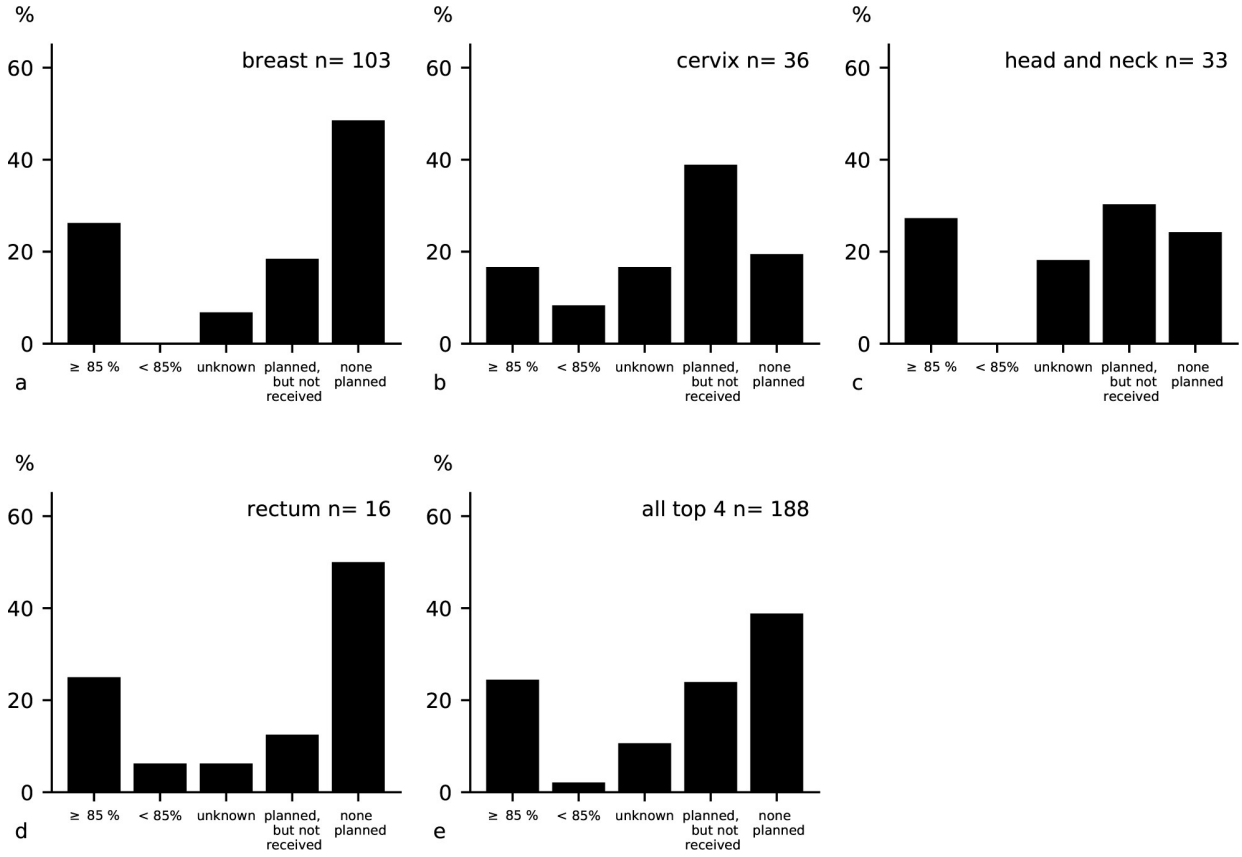


Fig 2. Completeness of radiotherapy according to local guidelines in top 4 cancer entities: (a) breast cancer stages 3 and 4; (b) cervical cancer stages 2–4 without single-shot; (c) head and neck cancer stages 2–4; (d) rectal cancer stages 2–4; (e) all 4 cancer entities together.

https://doi.org/10.1371/journal.pone.0219519.g002

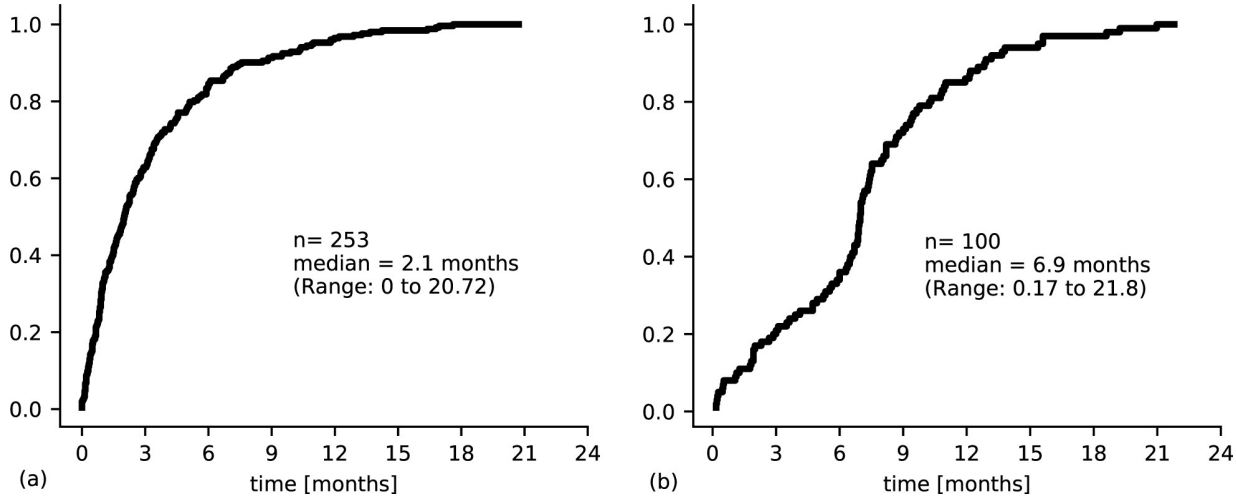


Fig 3. Cumulative probability of receiving chemotherapy (a) and radiotherapy (b) over time [in months].

https://doi.org/10.1371/journal.pone.0219519.g003

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)

Acknowledgments

We want to emphasize our gratitude to the staff of institutions collaborating with the AACCR, who significantly supported the process of this study by giving us access to patient files and by supporting to evaluate the patients medical history.

Author Contributions

Conceptualization: Jana Feuchtner, Assefa Mathewos, Genebo Timotewos, Eva Johanna Kantelhardt.

Data curation: Jana Feuchtner, Assefa Mathewos, Asmare Solomon, Genebo Timotewos, Abreha Aynalem, Tigeneh Wondemagegnehu.

Formal analysis: Jana Feuchtner, Andreas Wienke, Ahmedin Jemal, Eva Johanna Kantelhardt.

Funding acquisition: Eva Johanna Kantelhardt.

Investigation: Jana Feuchtner, Assefa Mathewos, Asmare Solomon, Genebo Timotewos, Fekadu Adugna, Adamu Addissie.

Methodology: Jana Feuchtner, Assefa Mathewos, Andreas Wienke, Adamu Addissie, Ahmedin Jemal, Eva Johanna Kantelhardt.

Project administration: Eva Johanna Kantelhardt.

Resources: Andreas Wienke, Ahmedin Jemal, Eva Johanna Kantelhardt.

Software: Jana Feuchtner, Andreas Wienke.

Supervision: Adamu Addissie, Ahmedin Jemal, Eva Johanna Kantelhardt.

Validation: Assefa Mathewos, Asmare Solomon, Genebo Timotewos, Abreha Aynalem, Tigeneh Wondemagegnehu, Fekadu Adugna, Mirko Griesel.

Visualization: Jana Feuchtner, Eva Johanna Kantelhardt.

Writing – original draft: Jana Feuchtner, Eva Johanna Kantelhardt.

Writing – review & editing: Jana Feuchtner, Assefa Mathewos, Asmare Solomon, Genebo Timotewos, Abreha Aynalem, Tigeneh Wondemagegnehu, Amha Gebremedhin, Fekadu Adugna, Mirko Griesel, Andreas Wienke, Adamu Addissie, Ahmedin Jemal, Eva Johanna Kantelhardt.

References

1. Harford JB. Barriers to overcome for effective cancer control in Africa. The Lancet Oncology. 2015; 16: e385–e393. https://doi.org/10.1016/S1470-2045(15)00160-6 PMID: 26248846
2. GLOBOCAN. Available: http://globocan.iarc.fr/old/burden.asp?selection_pop=1966&Text-p=Africa&selection_cancer=290&Text-c=All+cancers+excl.+non-melanoma+skin+cancer&pYear=23&type=0&window=1&submit=%C2%A0Execute%C2%A0. Accessed 24.07.18.
3. Demographic Components of Change—United Nations Population Division | Department of Economic and Social Affairs. Available: http://www.un.org/en/development/desa/population/theme/trends/dem-comp-change.shtml. Accessed 24.07.18.
4. https://esa.un.org/unpd/wpp/publications/files/key_findings_wpp_2015.pdf.
5. Cazap E, Magrath I, Kingham TP, Elzawawy A. Structural Barriers to Diagnosis and Treatment of Cancer in Low- and Middle-Income Countries. The Urgent Need for Scaling Up. J Clin Oncol. 2016; 34: 14–19. https://doi.org/10.1200/JCO.2015.61.9189 PMID: 26578618
6. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang X-S, et al. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). The Lancet; 385: 977–1010. https://doi.org/10.1016/S0140-6736(14)62038-9 PMID: 25467588
7. Jedy-Agba E, McCormack V, Adebamowo C, dos-Santos-Silva I. Stage at diagnosis of breast cancer in sub-Saharan Africa: a systematic review and meta-analysis. The Lancet Global Health. 2016; 4: e923–e935. https://doi.org/10.1016/S2214-109X(16)30259-5 PMID: 27855871
8. Sullivan R, Alatise OI, Anderson BO, Audisio R, Autier P, Aggarwal A, et al. Global cancer surgery. Delivering safe, affordable, and timely cancer surgery. The Lancet Oncology. 2015; 16: 1193–1224. https://doi.org/10.1016/S1470-2045(15)00223-5 PMID: 26427363
9. Gyorki DE, Muyco A, Kushner AL, Brennan MF, Kingham TP. Cancer surgery in low-income countries: an unmet need. Arch Surg. 2012; 147: 1135–1140. https://doi.org/10.1001/archsurg.2012.1265 PMID: 23248017
10. Kingham TP, Alatise OI, Vanderpuye V, Casper C, Abantanga FA, Kamara TB, et al. Treatment of cancer in sub-Saharan Africa. The Lancet Oncology. 2013; 14: e158–e167. https://doi.org/10.1016/S1470-2045(12)70472-2 PMID: 23561747
11. Abdel-Wahab M, Bourque J-M, Pynda Y, Iżewska J, van der Merwe D, Zubizarreta E, et al. Status of radiotherapy resources in Africa. An International Atomic Energy Agency analysis. The Lancet Oncology. 2013; 14: e168–e175. https://doi.org/10.1016/S1470-2045(12)70532-6 PMID: 23561748
12. Ethiopia Population (2018)—Worldometers. Available: http://www.worldometers.info/world-population/ethiopia-population/. Accessed 24.07.18.
13. Ethiopia: Regions, Major Cities & Towns—Population Statistics in Maps and Charts; 31.10.17. Available: https://www.citypopulation.de/Ethiopia. Accessed 24.07.18.
14. Collections—Quandl. Available: https://www.quandl.com/collections/health/physicians-density-per-1000-population-by-country. Accessed 26.08.16.
15. Woldeamanuel YW, Girma B, Teklu AM. Cancer in Ethiopia. The Lancet Oncology. 2013; 14: 289–290. https://doi.org/10.1016/S1470-2045(12)70399-6 PMID: 23561741
16. Barton MB, Frommer M, Shafiq J. Role of radiotherapy in cancer control in low-income and middle-income countries. The Lancet Oncology. 2006; 7: 584–595. https://doi.org/10.1016/S1470-2045(06)70759-8 PMID: 16814210
17. Timotewos G, Solomon A, Mathewos A, Addissie A, Bogale S, Wondemagegnehu T, et al. First data from a population based cancer registry in Ethiopia. Cancer Epidemiol. 2018; 53: 93–98. https://doi.org/10.1016/j.canep.2018.01.008 PMID: 29414637
18. CI5—Home. Available: http://ci5.iarc.fr/Default.aspx. Accessed 03.11.18.
19. TNM | UICC. Available: https://www.uicc.org/resources/tnm. Accessed 28.07.18.
20. Cervical Cancer Stages; 27.07.18. Available: https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/staged.html. Accessed 28.07.18.
21. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant Cyclophosphamide, Methotrexate, and Fluorouracil in Node-Positive Breast Cancer—The Results of 20 Years of Follow-up. N Engl J Med. 1995; 332:901–6. https://doi.org/10.1056/NEJM199504063321401 PMID: 7877646
22. Ethiopia—Life expectancy at birth 2016. Available: https://countryeconomy.com/demography/life-expectancy/ethiopia. Accessed 28.07.18.
23. Kantelhardt EJ, Moelle U, Begoihn M, Addissie A, Trocchi P, Yonas B, et al. Cervical cancer in Ethiopia: survival of 1,059 patients who received oncologic therapy. Oncologist. 2014; 19: 727–734. https://doi.org/10.1634/theoncologist.2013-0326 PMID: 24951611

24. Kantelhardt EJ, Zerche P, Mathewos A, Trocchi P, Addissie A, Aynalem A, et al. Breast cancer survival in Ethiopia: a cohort study of 1,070 women. Int J Cancer. 2014; 135: 702–709. https://doi.org/10.1002/ijc.28691 PMID: 24375396

25. Eber-Schulz P, Tariku W, Reibold C, Addissie A, Wickenhauser C, Fathke C, et al. Survival of breast cancer patients in rural Ethiopia. Breast Cancer Res Treat. 2018. https://doi.org/10.1007/s10549-018-4724-z PMID: 29479644

26. Shiferaw S, Addissie A, Gizaw M, Hirpa S, Ayele W, Getachew S, et al. Knowledge about cervical cancer and barriers toward cervical cancer screening among HIV-positive women attending public health centers in Addis Ababa city, Ethiopia. Cancer Med. 2018; 7: 903–912. https://doi.org/10.1002/cam4.1334 PMID: 29441700

27. Dye TD, Bogale S, Hobden C, Tilahun Y, Hechter V, Deressa T, et al. Complex care systems in developing countries: breast cancer patient navigation in Ethiopia. Cancer. 2010; 116: 577–585. https://doi.org/10.1002/cncr.24776 PMID: 20029968

28. Birhan W, Giday M, Teklehaymanot T. The contribution of traditional healers' clinics to public health care system in Addis Ababa, Ethiopia. A cross-sectional study. J Ethnobiol Ethnomed. 2011; 7: 39. https://doi.org/10.1186/1746-4269-7-39 PMID: 22132758

29. Grosse Frie K, Samoura H, Diop S, Kamate B, Traore CB, Malle B, et al. Why Do Women with Breast Cancer Get Diagnosed and Treated Late in Sub-Saharan Africa? Perspectives from Women and Patients in Bamako, Mali. Breast Care (Basel). 2018; 13: 39–43. https://doi.org/10.1159/000481087 PMID: 29950966

30. Harding R, Selman L, Agupio G, Dinat N, Downing J, Gwyther L, et al. The prevalence and burden of symptoms amongst cancer patients attending palliative care in two African countries. European Journal of Cancer. 2011; 47: 51–56. https://doi.org/10.1016/j.ejca.2010.08.003 PMID: 20822896

31. World Health Organization. WHO | WHO's cancer pain ladder for adults. Available: http://www.who.int/cancer/palliative/painladder/en/. Accessed 28.07.18.

32. Dedey F, Wu L, Ayettey H, Sanuade OA, Akingbola TS, Hewlett SA, et al. Factors Associated With Waiting Time for Breast Cancer Treatment in a Teaching Hospital in Ghana. Health Educ Behav. 2016; 43: 420–427. https://doi.org/10.1177/1090198115620417 PMID: 27091222

33. Otieno ES, Micheni JN, Kimende SK, Mutai KK. Delayed presentation of breast cancer patients. East Afr Med J. 2010; 87: 147–150. PMID: 23057289

34. Grosse Frie K, Kamaté B, Traoré CB, Ly M, Mallé B, Coulibaly B, et al. Factors associated with time to first healthcare visit, diagnosis and treatment, and their impact on survival among breast cancer patients in Mali. PLoS One. 2018; 13: e0207928. https://doi.org/10.1371/journal.pone.0207928 PMID: 30496219

35. Bhatia RK, Rayne S, Rate W, Bakwenabatsile L, Monare B, Anakwenze C, et al. Patient Factors Associated With Delays in Obtaining Cancer Care in Botswana. J Glob Oncol. 2018; 4: 1–13. https://doi.org/10.1200/JGO.18.00088 PMID: 30199305

36. Arndt V, Sturmer T, Stegmaier C, Ziegler H, Becker A, Brenner H. Provider delay among patients with breast cancer in Germany: a population-based study. J Clin Oncol. 2003; 21: 1440–1446. https://doi.org/10.1200/JCO.2003.08.071 PMID: 12697864

37. Birhanu Z, Abdissa A, Belachew T, Deribew A, Segni H, Tsu V, et al. Health seeking behavior for cervical cancer in Ethiopia. A qualitative study. Int J Equity Health. 2012; 11: 83. https://doi.org/10.1186/1475-9276-11-83 PMID: 23273140

38. Mostert S, Arora RS, Arreola M, Bagai P, Friedrich P, Gupta S, et al. Abandonment of treatment for childhood cancer. Position statement of a SIOP PODC Working Group. The Lancet Oncology. 2011; 12: 719–720. https://doi.org/10.1016/S1470-2045(11)70128-0 PMID: 21719348

39. Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer. 2005; 104: 1129–1137. https://doi.org/10.1002/cncr.21324 PMID: 16080176

40. Rosenblatt E, Fidarova E, Zubizarreta EH, Barton MB, Jones GW, Mackillop WJ, et al. Radiotherapy utilization in developing countries: An IAEA study. Radiother Oncol. 2018; 128: 400–405. https://doi.org/10.1016/j.radonc.2018.05.014 PMID: 29859755

41. Denny L, Sanjose S de, Mutebi M, Anderson BO, Kim J, Jeronimo J, et al. Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries. The Lancet. February///25; 389: 861–870. https://doi.org/10.1016/S0140-6736(16)31795-0

Original Article

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

Tobias Paul Seraphin, MD [1]; Walburga Yvonne Joko-Fru, MD[2,3]; Lucia Hämmerl, MD[1]; Mirko Griesel, MD [1]; Nikolaus Christian Simon Mezger, MD [1]; Jana Cathrin Feuchtner, MD[1]; Innocent Adoubi, MD[4,5]; Marcel Dieu-Donné Egué, BSc[6]; Nathan Okerosi[7]; Henry Wabinga, MD[8]; Rolf Hansen, BBA[9]; Samukeliso Vuma, MD[10]; Cesaltina Lorenzoni, PhD[11,12]; Bourama Coulibaly, MD[13]; Sévérin W. Odzebe, MD[14]; Nathan Gyabi Buziba, MD[15,16]; Abreha Aynalem, MD[17,*]; Biying Liu, MPH[2]; Daniel Medenwald, MD[1]; Rafael T. Mikolajczyk, MD[1]; Jason Alexander Efstathiou, MD[18,19]; Donald Maxwell Parkin, MD [3,20]; Ahmedin Jemal, PhD [21]; and Eva Johanna Kantelhardt, MD [1,22]

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

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

Corresponding Author: Eva J. Kantelhardt, MD, Institute of Medical Epidemiology, Biometrics and Informatics, Martin Luther University Halle-Wittenberg, Magdeburgerstrasse 8, 06097 Halle (Saale), Germany (eva.kantelhardt@uk-halle.de).

[1]Institute of Medical Epidemiology, Biometrics and Informatics, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany; [2]African Cancer Registry Network, International Network for Cancer Treatment and Research African Registry Programme, Oxford, United Kingdom; [3]Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom; [4]Department of Immunology, Haematology and Oncology, University of Felix Houphouet-Boigny, Abidjan, Côte d'Ivoire; [5]Abidjan Cancer Registry, Programme National de Lutte contre le Cancer, Ministry of Health, Abidjan, Côte d'Ivoire; [6]Cotonou Cancer Registry, Ministry of Health, Cotonou, Benin; [7]National Cancer Registry, Kenya Medical Research Institute, Nairobi, Kenya; [8]Kampala Cancer Registry, Department of Pathology, School of Biomedical Sciences, College of Health Sciences, Makerere University, Kampala, Uganda; [9]Namibia National Cancer Registry, Cancer Association of Namibia, Windhoek, Namibia; [10]Bulawayo Cancer Registry, Department of Radiotherapy, Mpilo Hospital, Bulawayo, Zimbabwe; [11]National Cancer Control Programme, Ministry of Health, Maputo, Mozambique; [12]Maputo Cancer Registry, Department of Pathology, Hospital Central de Maputo, Maputo, Mozambique; [13]Cancer Registry of Bamako, Hôpital National du Point G, Bamako, Mali; [14]Cancer Registry of Brazzaville, University Hospital Brazzaville, Brazzaville, Republic of Congo; [15]Eldoret Cancer Registry, Moi Teaching Hospital, Eldoret, Kenya; [16]Department of Haematology and Blood Transfusion, Moi University School of Medicine, Eldoret, Kenya; [17]Addis Ababa City Cancer Registry, Radiotherapy Center, Addis-Ababa-University, Addis Ababa, Ethiopia; [18]Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts; [19]Claire and John Bertucci Center for Genitourinary Cancers Multidisciplinary Clinic, Massachusetts General Hospital, Boston, Massachusetts; [20]Cancer Surveillance Unit, International Agency for Research on Cancer, Lyon, France; [21]Surveillance & Health Equity Science Department, American Cancer Society, Atlanta, Georgia; [22]Department of Gynecology, University Hospital Halle, Martin Luther University Halle-Wittenberg, Halle, Germany

See editorial on pages 4131-4132, this issue.

The last 2 authors contributed equally to this article.

The staff of all contributing registries of the African Cancer Registry Network are gratefully acknowledged.

Co-author Dr. Abreha Aynalem, MD, died April 9, 2021.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33818, **Received:** October 31, 2020; **Revised:** April 17, 2021; **Accepted:** May 18, 2021, **Published online** July 30, 2021 in Wiley Online Library (wileyonlinelibrary.com)

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

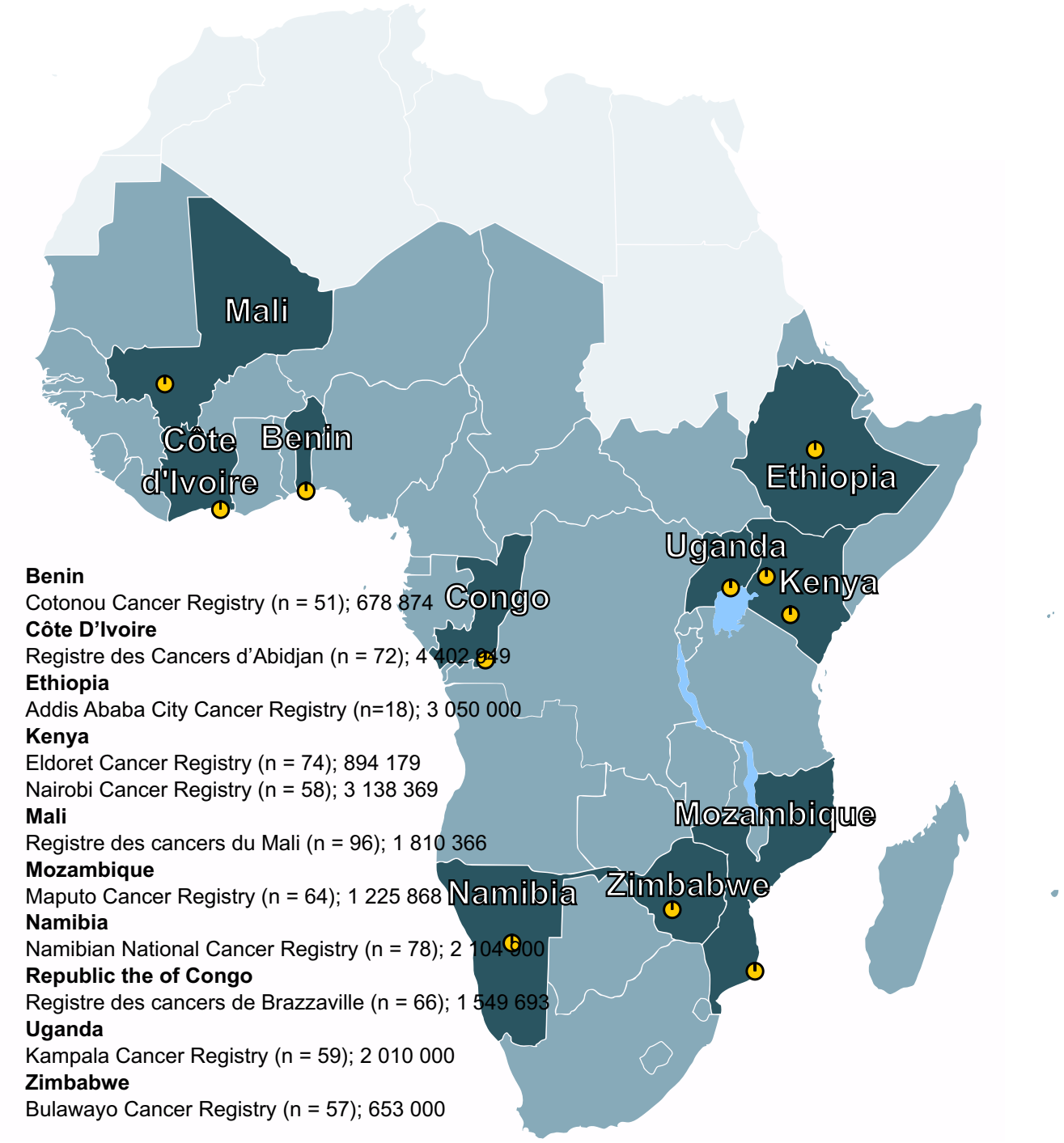


Figure 1. Countries of participating cancer registries. Countries of participating population-based cancer registries are highlighted along with the names of the registries, the number of included patients (n), and the population of each coverage area (persons).

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).

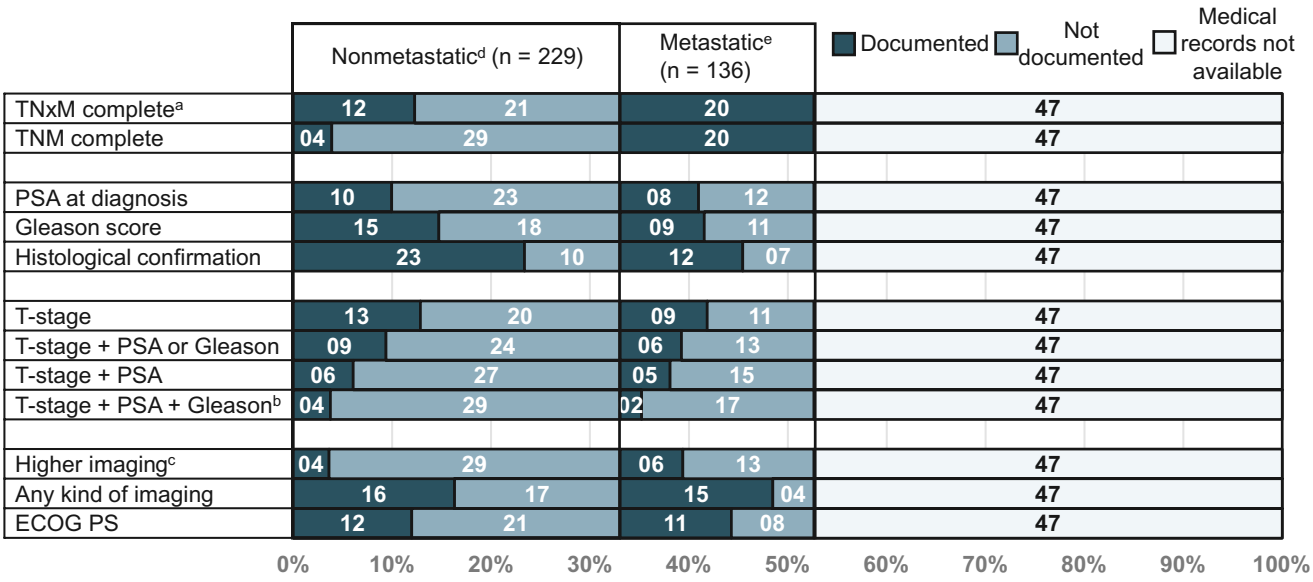


Figure 2. Availability of diagnostic information for patients with prostate cancer in the total population-based cohort (n = 693). [a]Nx included. [b]Main prognostic factors according to the 2017 National Comprehensive Cancer Network guidelines. [c]For example, computed tomography, magnetic resonance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

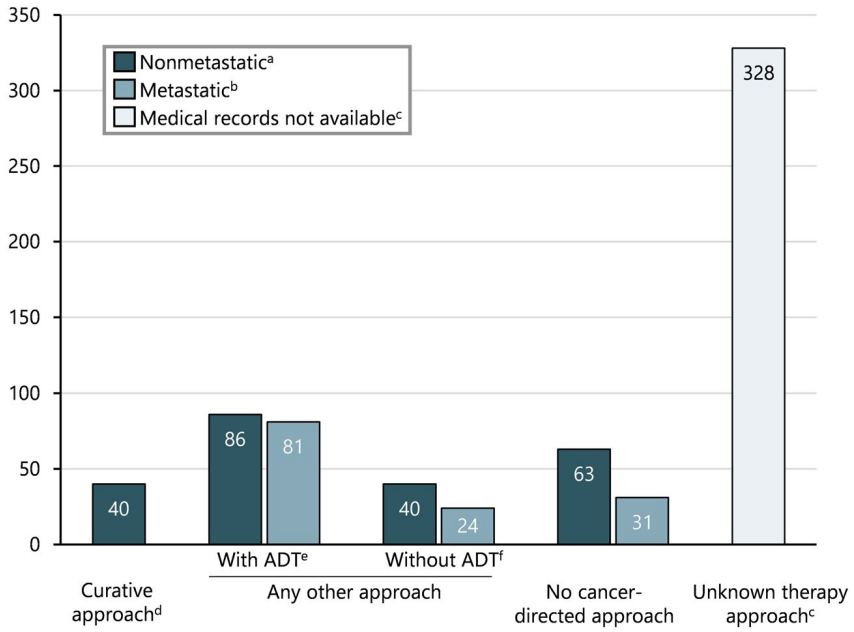


Figure 3. Primary treatment approach by identified M stage in the total population-based cohort (n = 693). [a]The nonmetastatic subgroup (n = 229) comprised all patients without a pathological or clinical suggestion of metastasis (M0), including patients with an unknown lymph node status (Nx M0). [b]The 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.

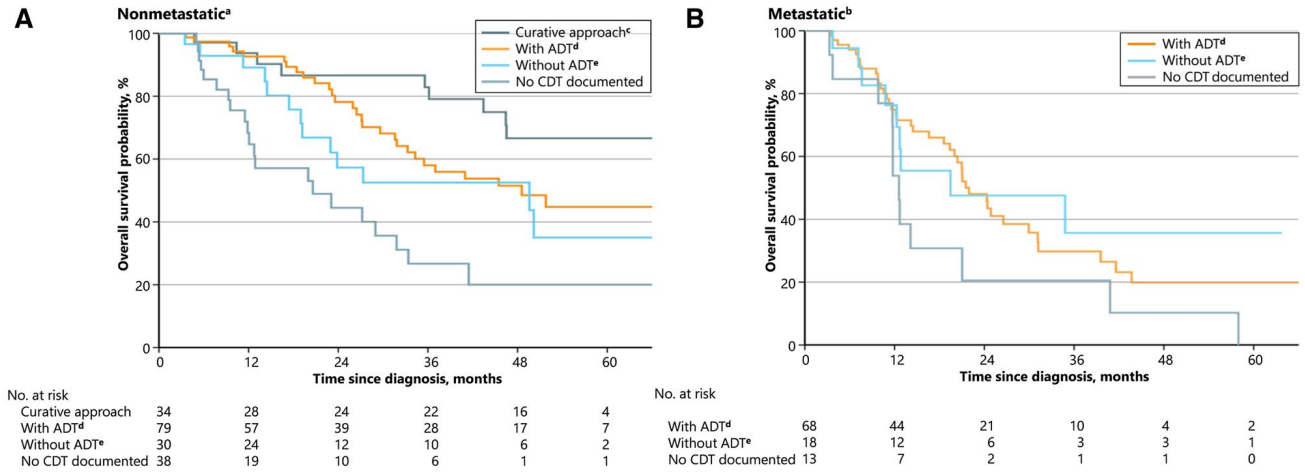


Figure 4. Overall survival of patients from the traced cohort with at least 3 months of survival stratified by M stage: differences according to the treatment approach. [a]These patients surviving at least 3 months from the nonmetastatic subgroup (n = 181) included all patients without a pathological 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

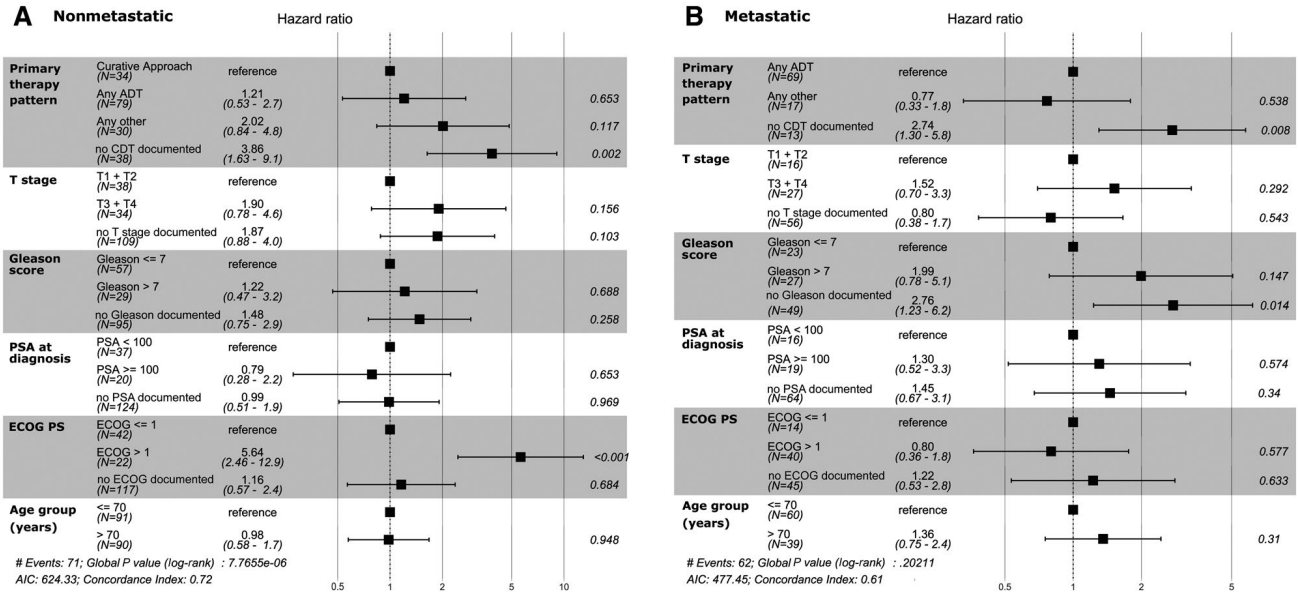


Figure 5. Forest plots showing the influence of primary treatment patterns on the survival of (A) patients with nonmetastatic prostate cancer[a] and (B) patients with metastatic prostate cancer.[b] The hazard ratios and 95% confidence intervals are the results of a multivariable Cox regression model 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.

FUNDING SUPPORT

Eva J. Kantelhardt was supported by intramural funding from the Research Department of the American Cancer Society (contract 43359). Tobias Paul Seraphin was supported by Studienstiftung des Deutschen Volkes eV through his regular scholarship and was a recipient of a 8-month Halle-Oxford exchange fellowship grant within European Union/European Social Fund–funded research (International Research Network Biology of Disease and Molecular Medicine; ZS/2016/08/80642) from Martin Luther University Halle-Wittenberg. Jana Feuchtner was given a doctorate stipend by the Bayer Foundation. Lucia Hämmerl was supported by Bischöfliche Studienförderung Cusanuswerk through her regular scholarship. Nikolaus C. S. Mezger was supported by the German Academic Exchange Service,

which is financed by the Federal Ministry of Education and Research and received support from the Roland Ernst Stiftung für Gesundheitswesen. None of the funders/sponsors had a role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; in the preparation, review, or approval of the manuscript; or in the decision to submit the manuscript for publication.

CONFLICT OF INTEREST DISCLOSURES

Jason A. Efstathiou reports consulting fees from Boston Scientific, Blue Earth Diagnostics, and AstraZeneca and participation on advisory boards for Roivant Pharma, Myovant Sciences, Merck, Janssen, and Bayer HealthCare. The other authors made no disclosures.

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.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424. doi:10.3322/caac.21492
2. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. *Lancet Oncol*. 2012;13:790-801. doi:10.1016/S1470-2045(12)70211-5
3. Seraphin TP, Joko-Fru WY, Kamaté B, et al. Rising prostate cancer incidence in sub-Saharan Africa: a trend analysis of data from the African Cancer Registry Network. *Cancer Epidemiol Biomarkers Prev*. 2021;30:158-165. doi:10.1158/1055-9965.EPI-20-1005
4. Jemal A, Bray F, Forman D, et al. Cancer burden in Africa and opportunities for prevention. *Cancer*. 2012;118:4372-4384. doi:10.1002/cncr.27410
5. Baratedi WM, Tshiamo WB, Mogobe KD, McFarland DM. Barriers to prostate cancer screening by men in sub-Saharan Africa: an integrated review. *J Nurs Scholarsh*. 2020;52:85-94. doi:10.1111/jnu.12529
6. Jalloh M, Niang L, Ndoye M, Labou I, Gueye SM. Prostate cancer in sub Saharan Africa. *J Nephrol Urol Res*. 2013;1:15-20. doi:10.12970/2310-984X.2013.01.01.4
7. DeSantis CE, Siegel RL, Sauer AG, et al. Cancer statistics for African Americans, 2016: progress and opportunities in reducing racial disparities. *CA Cancer J Clin*. 2016;66:290-308. doi:10.3322/caac.21340
8. McGinley KF, Tay KJ, Moul JW. Prostate cancer in men of African origin. *Nat Rev Urol*. 2016;13:99-107. doi:10.1038/nrurol.2015.298
9. DeRouen MC, Schupp CW, Koo J, et al. Impact of individual and neighborhood factors on disparities in prostate cancer survival. *Cancer Epidemiol*. 2018;53:1-11. doi:10.1016/j.canep.2018.01.003
10. Krimphove MJ, Cole AP, Fletcher SA, et al. Evaluation of the contribution of demographics, access to health care, treatment, and tumor characteristics to racial differences in survival of advanced prostate cancer. *Prostate Cancer Prostatic Dis*. 2019;22:125-136. doi:10.1038/s41391-018-0083-4
11. NCCN Harmonized Guidelines for Sub-Saharan Africa: Prostate Cancer. Version 2.2017. National Comprehensive Cancer Network. Accessed June 25, 2018. https://www.nccn.org/global/what-we-do/harmonized-guidelines
12. Mottet N, van den Bergh RCN, Briers E, et al. EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. EAU Guidelines Office; 2018.
13. Finesse AM, Somdyala N, Chokunonga E, Parkin DM, eds. Standard Procedure Manual for Population-Based Cancer Registries in Sub Saharan Africa. 2nd ed. African Cancer Registry Network. Published 2015. Accessed November 21, 2018. https://afcrn.org/index.php/resources2/53-standard-procedure-manual/131-sop
14. Amin MB, Greene FL, Edge SB, eds. AJCC Cancer Staging Manual. 8th ed. Springer; 2017.
15. Piñeros M, Parkin DM, Ward K, et al. Essential TNM: a registry tool to reduce gaps in cancer staging information. *Lancet Oncol*. 2019;20:e103-e111. doi:10.1016/S1470-2045(18)30897-0
16. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. *Eur J Cancer*. 2004;40:2307-2316. doi:10.1016/j.ejca.2004.07.002
17. Noone A, Howlader N, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2015. National Cancer Institute; 2018.
18. Abdel-Wahab M, Bourque J-M, Pynda Y, et al. Status of radiotherapy resources in Africa: an International Atomic Energy Agency analysis. *Lancet Oncol*. 2013;14:e168-e175. doi:10.1016/S1470-2045(12)70532-6
19. Kanavos P. The rising burden of cancer in the developing world. *Ann Oncol*. 2006;17(suppl 8):viii15-viii23. doi:10.1093/annonc/mdl983
20. Prostate Cancer Early Detection: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Version 2.2018. National Comprehensive Cancer Network. Accessed December 16, 2018. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1459
21. Potosky AL. The role of increasing detection in the rising incidence of prostate cancer. *JAMA*. 1995;273:548. doi:10.1001/jama.1995.03520310046028
22. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;157:120-134. doi:10.7326/0003-4819-157-2-201207170-00459
23. Brawley OW. Trends in prostate cancer in the United States. *J Natl Cancer Inst Monogr*. 2012;2012:152-156. doi:10.1093/jncimonographs/lgs035
24. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. *JAMA*. 2009;302:1685-1692. doi:10.1001/jama.2009.1498
25. Badmus TA, Adesunkanmi A-RK, Yusuf BM, et al. Burden of prostate cancer in southwestern Nigeria. *Urology*. 2010;76:412-416. doi:10.1016/j.urology.2010.03.020
26. Heyns CF, Fisher M, Lecuona A, van der Merwe A. Prostate cancer among different racial groups in the Western Cape: presenting features and management. *S Afr Med J*. 2011;101:267-270. doi:10.7196/SAMJ.4420

27. Asamoah FA, Yarney J, Awasthi S, et al. Contemporary radiation treatment of prostate cancer in Africa: a Ghanaian experience. *J Glob Oncol*. 2018;4:1-13. doi:10.1200/JGO.17.00234
28. Meara JG, Leather AJM, Hagander L, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. *Lancet*. 2015;386:569-624. doi:10.1016/S0140-6736(15)60160-X
29. Efstathiou JA, Heunis M, Karumekayi T, et al. Establishing and delivering quality radiation therapy in resource-constrained settings: the story of Botswana. *J Clin Oncol*. 2016;34:27-35. doi:10.1200/JCO.2015.62.8412
30. Kingham TP, Alatise OI, Vanderpuye V, et al. Treatment of cancer in sub-Saharan Africa. *Lancet Oncol*. 2013;14:e158-e167. doi:10.1016/S1470-2045(12)70472-2
31. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. 2018;391:1023-1075. doi:10.1016/S0140-6736(17)33326-3
32. American Cancer Society. Cancer Facts & Figures 2018. American Cancer Society; 2018.
33. Barry MJ. Screening for prostate cancer—the controversy that refuses to die. *N Engl J Med*. 2009;360:1351-1354. doi:10.1056/NEJMe0901166
34. Jemal A, Fedewa SA, Ma J, et al. Prostate cancer incidence and PSA testing patterns in relation to USPSTF screening recommendations. *JAMA*. 2015;314:2054-2061. doi:10.1001/jama.2015.14905

bjh research paper

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

Nikolaus C. S. Mezger,[1] Jana Feuchtner,[1] Mirko Griesel,[1] Lucia Hämmerl,[1] Tobias P. Seraphin,[1] Annelle Zietsman,[2,3] Jean-Félix Péko,[2,4] Fisihatsion Tadesse,[2,5] Nathan G. Buziba,[2,6] Henry Wabinga,[2,7] Mary Nyanchama,[2,8] Margaret Z. Borok,[2,9] Mamadou Kéita,[2,10] Guy N'da,[2,11] Cesaltina F. Lorenzoni,[2,12] Marie-Thérèse Akele-Akpo,[2,13] Cornelia Gottschick,[1] Mascha Binder,[14] Jörg Mezger,[15] Ahmedin Jemal,[16] Donald M. Parkin,[2,17] Claudia Wickenhauser[18] and Eva J. Kantelhardt[1,19]

[1]Institute of Medical Epidemiology, Biometrics and Informatics, Martin-Luther-University Halle-Wittenberg, Halle, Germany, [2]African Cancer Registry Network, Oxford, UK, [3]Dr AB May Cancer Care Centre, Windhoek, Namibia, [4]Registre des Cancers de Brazzaville, Brazzaville, Republic of the Congo, [5]Division of Hematology, Department of Internal Medicine, University and Black Lion Hospital, Addis Ababa, Ethiopia, [6]Eldoret Cancer Registry,Moi Teaching and Referral Hospital, Eldoret, Kenya, [7]Kampala Cancer Registry,Makerere University School of Medicine, Kampala, Uganda, [8]National Cancer Registry,Kenya Medical Research Institute, Nairobi, Kenya, [9]Zimbabwe National Cancer Registry, Harare, Zimbabwe, [10]Service du Laboratoire d'Anatomie et Cytologie Pathologique, CHU du point G, Bamako, Mali, [11]Registre des Cancers d'Abidjan, Abidjan, Côte d'Ivoire, [12]Departamento de Patologia, Faculdade de Medicina Universidade Eduardo Mondlane,Maputo, Mozambique, [13]Département d'Anatomo-Pathologie, Faculté des Sciences de la Santé,Cotonou, Benin, [14]Department of Internal Medicine IV, Oncology and Hematology, Martin-Luther-University Halle-Wittenberg, Halle,

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.

 British Journal of Haematology, 2020, **190,** 209–221 First published online 17 March 2020 doi: 10.1111/bjh.16575

Germany, [15]*medGAIN, Karlsruhe, Germany,* [16]*Surveillance and Health Services Research, American Cancer Society, Atlanta, GA, USA,* [17]*Nuffield Department of Population Health, University of Oxford, Oxford, UK,* [18]*Institute of Pathology, Martin-Luther-University Halle-Wittenberg, Halle, Germany and* [19]*Department of Gynaecology, Martin-Luther-University Halle-Wittenberg, Halle, Germany*

Received 16 December 2019; revised 16 February 2020; accepted for publication 20 February 2020

Correspondence: Eva Johanna Kantelhardt, Institute of Medical Epidemiology, Biometrics and Informatics, Martin-Luther-University Halle-Wittenberg, Magdeburger Str 8, 06112 Halle (Saale), Germany
E-mail: eva.kantelhardt@uk-halle.de

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

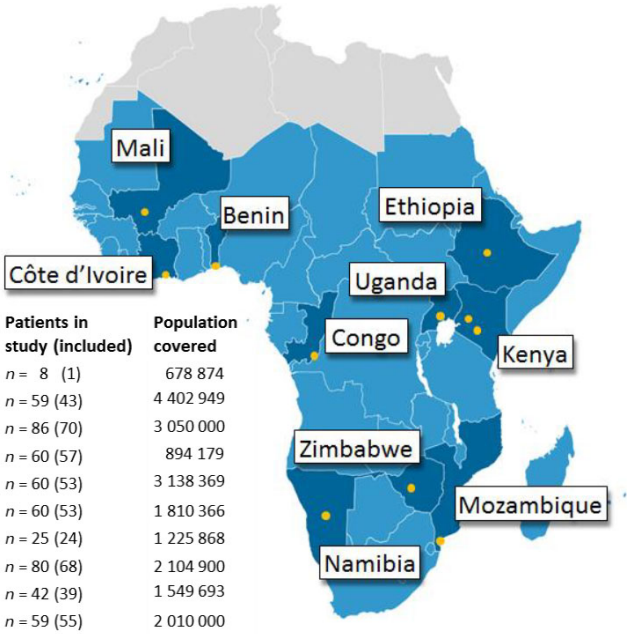
registries due to lack of patients. In total, 1068 patients were available in the registry databases. We assessed prevalence of adequate care from medical records among a random sample that could be assessed within feasible time and efforts in the given setting. We intended to draw conclusions for an 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)

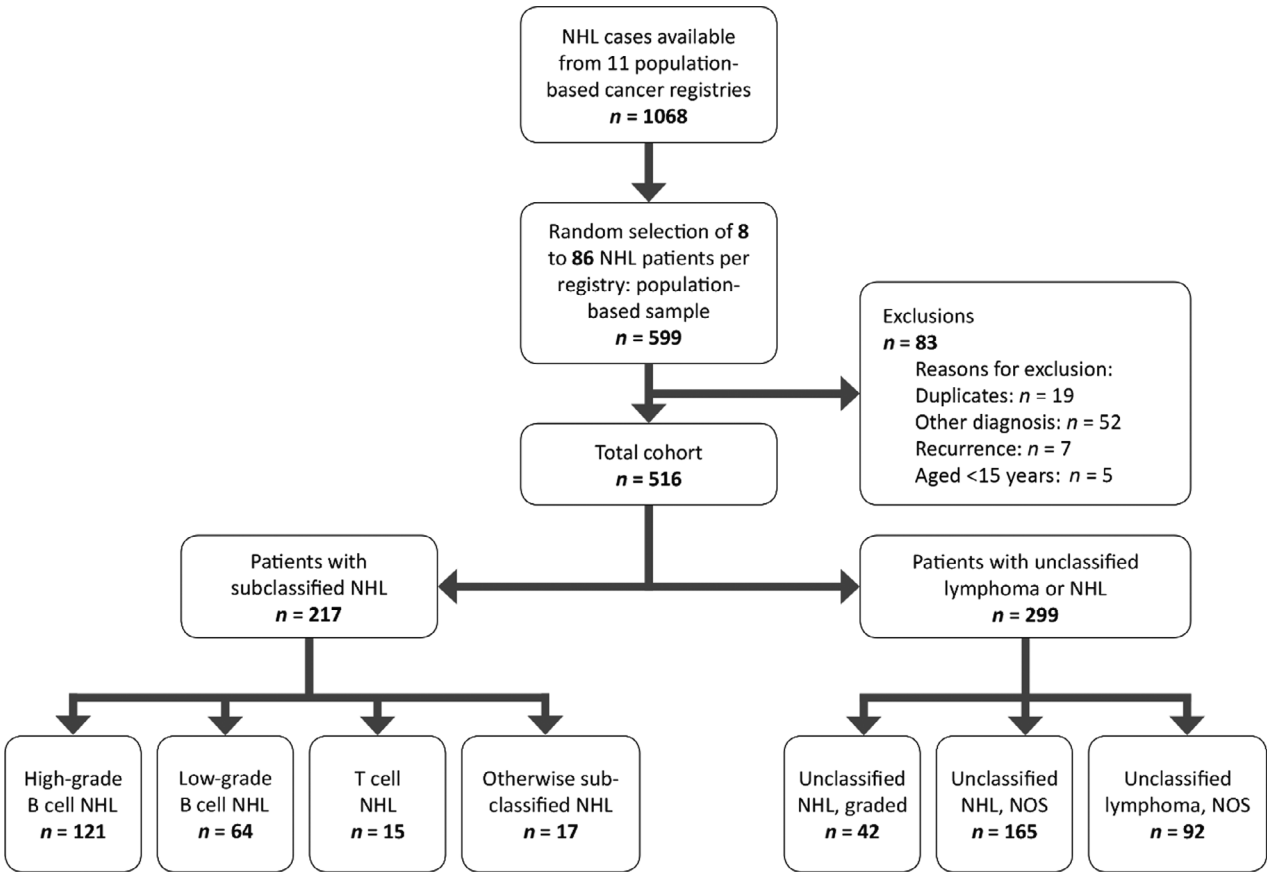


Fig. 2. Flowchart of study population. Stratified by non-Hodgkin lymphoma groups. NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

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,

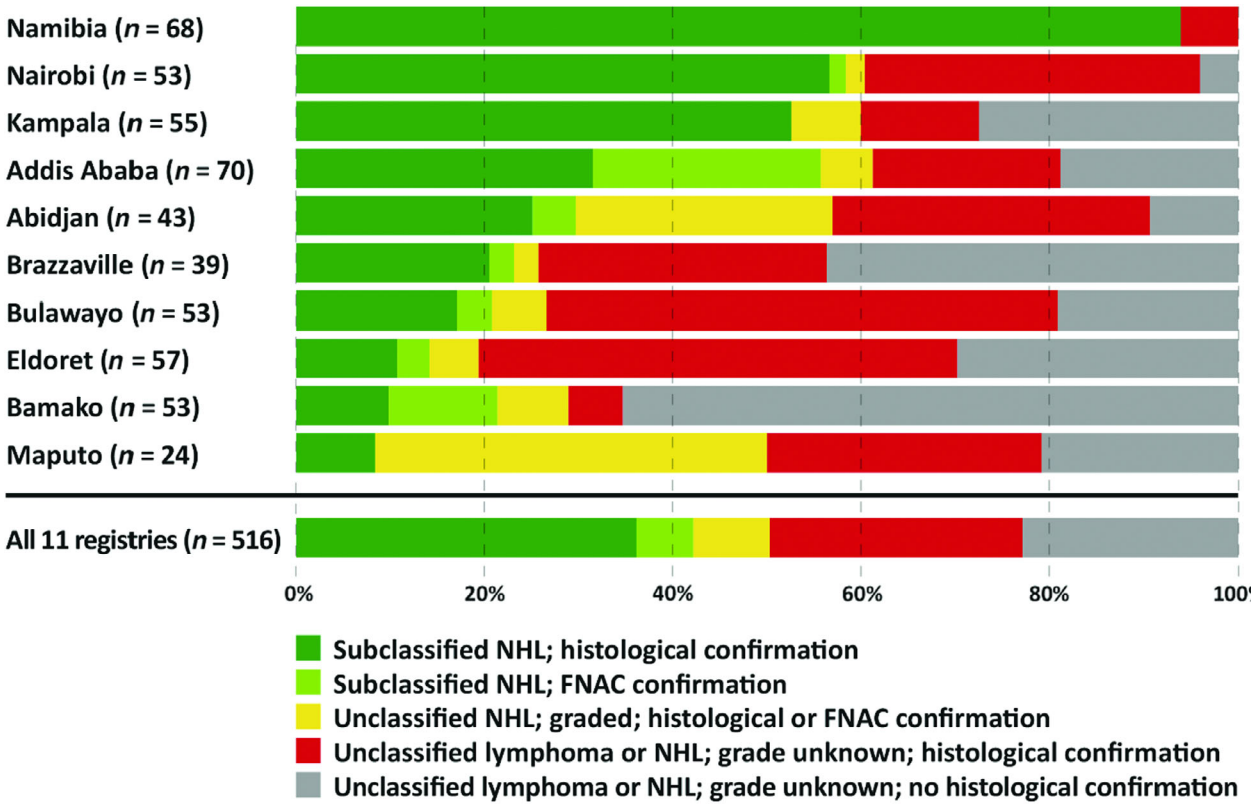


Fig. 3. Quality of pathological diagnosis. Stratified by population-based cancer registries, in order of quality of pathological diagnosis. With respect to non-Hodgkin lymphoma (NHL) subclassification, grade and diagnostic modality [according to National Comprehensive Cancer Network guidelines harmonised 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

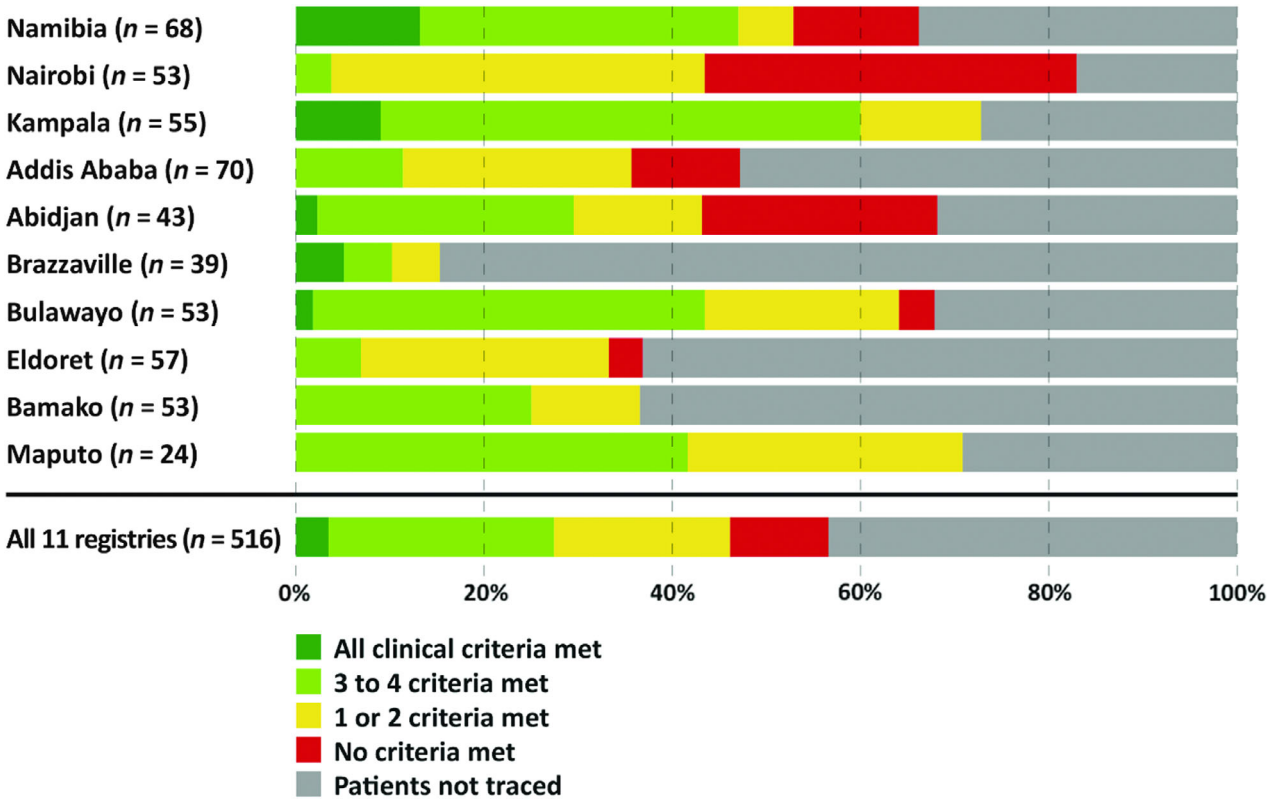


Fig. 4. Completeness of clinical diagnostic criteria. Stratified by population-based cancer registries, in order of Figure 3. With respect to information on Eastern Cooperative Oncology Group Performance Status, B symptoms, human immunodeficiency virus status, stage and any imaging [according to National 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.

Acknowledgements

We appreciate the sustained support of Gerhard Faller, and Biying Liu in revising the paper. We were supported by Intramural Funding from the Research Department of the American Cancer Society (Contract No. 43359) and the German Ministry for Economic and Development Cooperation (BMZ) through the ESTHER University and Hospital Partnership Initiative of German International Cooperation (GIZ, Project No. 13.2238.7-004.41). Nikolaus C.S. Mezger received a doctorate stipend from the German Academic Exchange Service (DAAD) and Roland Ernst Stiftung für Gesundheitswesen, Lucia Hämmerl received a doctorate stipend from the Bischöfliche Studienförderung Cusanuswerk, Jana

Feuchtner received a doctorate stipend from the Bayer Foundation. The sponsors of this study are public or non-profit organisations that support science in general. They had no role in gathering, analysing, or interpreting the data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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.

References

Adesina, A., Chumba, D., Nelson, A.M., Orem, J., Roberts, D.J., Wabinga, H., Wilson, M. & Rebbeck, T.R. (2013) Improvement of pathology in sub-Saharan Africa. *The Lancet Oncology*, **14**, e152–e157.

April, F., Percy, C., Jack, A., Shanmugaratnam, K., Sobin, L., Parkin, D.M. & Whelan, S. (2013) International Classification of Diseases for Oncology. Third Edition. First Revision. http://apps.who.int/iris/bitstream/handle/10665/96612/9789241548496_eng.pdf;jsessionid=6D582B25CFBBF5C08F80E194A38F2023?sequence=1, 10 Sep 2019.

Armitage, J.O. (2013) The aggressive peripheral T-cell lymphomas: 2013. *American journal of hematology*, **88**, 910–918.

Ayers, L.W., Akin Abayomi, E., Adebamowo, C., Chumba, D.K., Iliyasu, Y., Naresh, K.N., NDung'u, J.R., Perner, Y., Stevens, W. & Tumwine, L.K. (2012) HIV/AIDS-related non-Hodgkin's lymphomas and confounders. Preliminary report of the Sub-Saharan Africa Lymphoma Consortium (SSALC). *Infectious agents and cancer*, **7**, P11.

Bateganya, M.H., Stanaway, J., Brentlinger, P.E., Magaret, A.S., Wald, A., Orem, J. & Casper, C. (2011) Predictors of survival after a diagnosis of non-Hodgkin lymphoma in a resource-limited setting. A retrospective study on the impact of HIV infection and its treatment. *Journal of acquired immune deficiency syndromes*, **56**, 312–319.

Benediktsson, H., Whitelaw, J. & Roy, I. (2007) Pathology services in developing countries. A challenge. *Archives of Pathology & Laboratory Medicine*, **131**, 1636–1639.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A. & Jemal, A. (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, **68**, 394–424.

Buyego, P., Nakiyingi, L., Ddungu, H., Walimbwa, S., Nalwanga, D., Reynolds, S.J. & Parkes-Ratanshi, R. (2017) Possible misdiagnosis of HIV associated lymphoma as tuberculosis among patients attending Uganda Cancer Institute. *AIDS research and therapy*, **14**, 13.

Cainelli, F., Tanko, M.N. & Vento, S. (2010) The challenge of lymphomas in sub-Saharan Africa. *The Lancet Oncology*, **11**, 610–611.

Carbone, A., Vaccher, E., Gloghini, A., Pantanowitz, L., Abayomi, A., de Paoli, P. & Franceschi, S. (2014) Diagnosis and management of

lymphomas and other cancers in HIV-infected patients. *Nature reviews. Clinical oncology*, **11**, 223–238.

Cesarman, E. (2013) Pathology of lymphoma in HIV. *Current opinion in oncology*, **25**, 487–494.

Cesarman, E., Chang, Y., Moore, P.S., Said, J.W. & Knowles, D.M. (1995) Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. *The New England journal of medicine*, **332**, 1186–1191.

Chang, C., Huang, S.-W., Su, I.-J. & Chang, K.-C. (2014) Hematopathologic discrepancies between referral and review diagnoses: a gap between general pathologists and hematopathologists. *Leukemia & lymphoma*, **55**, 1023–1030.

Cheson, B.D., Fisher, R.I., Barrington, S.F., Cavalli, F., Schwartz, L.H., Zucca, E. & Lister, T.A. (2014) Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *Journal of clinical oncology*, **32**, 3059–3068.

Chokunonga, E., Borok, M.Z., Chirenje, Z.M., Nyakabau, A.M. & Parkin, D.M. (2013) Trends in the incidence of cancer in the black population of Harare, Zimbabwe 1991–2010. *International journal of cancer*, **133**, 721–729.

Clarke, C.A., Glaser, S.L., Dorfman, R.F., Bracci, P.M., Eberle, E. & Holly, E.A. (2004) Expert review of non-Hodgkin's lymphomas in a population-based cancer registry: Reliability of diagnosis and subtype classifications. *Cancer epidemiology, biomarkers & prevention*, **13**, 138–143.

Cook, L., Melamed, A., Yaguchi, H. & Bangham, C.R. (2017) The impact of HTLV-1 on the cellular genome. *Current opinion in virology*, **26**, 125–131.

Crawford, D.H., Rickinson, A. & Johannessen, I. (2014) Cancer virus. The story of Epstein-Barr Virus. Oxford University Press, Oxford.

Crocker-Buque, T. & Pollock, A.M. (2015) Appraising the quality of sub-Saharan African cancer registration systems that contributed to GLOBOCAN 2008. A review of the literature and critical appraisal. *Journal of the Royal Society of Medicine*, **108**, 57–67.

Finesse, Am, Somdyala, N., Chokunonga, E. & Parkin, D.M. Standard Procedure Manual. For Population-Based Cancer Registries in sub-Saharan Africa. Version II. http://afcrn.org/resources/51-afcrndatabase/131-sop, 6 Sep 2019.

Gopal, S., Wood, W.A., Lee, S.J., Shea, T.C., Naresh, K.N., Kazembe, P.N., Casper, C., Hesseling, P.B. & Mitsuyasu, R.T. (2012) Meeting the challenge of hematologic malignancies in sub-Saharan Africa. *Blood*, **119**, 5078–5087.

Gopal, S., Fedoriw, Y., Kaimila, B., Montgomery, N.D., Kasonkanji, E., Moses, A., Nyasosela, R., Mzumara, S., Varela, C., Chikasema, M., Makwakwa, V., Itimu, S., Tomoka, T., Kamiza, S., Dhungel, B.M., Chimzimu, F., Kampani, C., Krysiak, R., Richards, K.L., Shea, T.C. & Liomba, N.G. (2016) CHOP Chemotherapy for Aggressive Non-Hodgkin Lymphoma with and without HIV in the Antiretroviral Therapy Era in Malawi. *PLoS ONE*, **11**, e0150445.

Grulich, A.E., van Leeuwen, M.T., Falster, M.O. & Vajdic, C.M. (2007) Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *The Lancet*, **370**, 59–67.

Hallek, M. (2017) Chronic lymphocytic leukemia. 2017 update on diagnosis, risk stratification, and treatment. *American journal of hematology*, **92**, 946–965.

Herrera, A.F., Crosby-Thompson, A., Friedberg, J.W., Abel, G.A., Czuczman, M.S., Gordon, L.I., Kaminski, M.S., Millenson, M.M., Nademanee, A.P., Niland, J.C., Rodig, S.J., Rodriguez, M.A., Zelenetz, A.D. & LaCasce, A.S. (2014) Comparison of referring and final pathology for patients with T-cell lymphoma in the National Comprehensive Cancer Network. *Cancer*, **120**, 1993–1999.

Howlader, N., Noone, Am, Krapcho, M., Miller, D., Brest, A., Yu, M., Ruhl, J., Tatalovich, Z., Mariotto, A., Lewis, C.H.S.,Feuer, E.J. & Cronin, K.A. (2019) SEER Cancer Statistics Review, 1975–2016. Based on November 2018 SEER data submission. https://seer.cancer.gov/csr/1975_2016/, 6 Sep 2019.

LaCasce, A.S., Kho, M.E., Friedberg, J.W., Niland, J.C., Abel, G.A., Rodriguez, M.A., Czuczman, M.S., Millenson, M.M., Zelenetz, A.D. & Weeks, J.C. (2008) Comparison of referring and final pathology for patients with non-Hodgkin's lymphoma in the National Comprehensive Cancer Network. *Journal of clinical oncology*, **26**, 5107–5112.

Lage, L.A.d.P.C., Cabral, T.C.d.S., Costa, R.d.O., Gonçalves, M.d.C., Levy, D., Zerbini, M.C.N. & Pereira, J. (2015) Primary nodal peripheral T-cell lymphomas: diagnosis and therapeutic considerations. *Revista brasileira de hematologia e hemoterapia*, **37**, 277–284.

Lemos, M.P., Taylor, T.E., McGoldrick, S.M., Molyneux, M.E., Menon, M., Kussick, S., Mkhize, N.N., Martinson, N.A., Stritmatter, A. & Randolph-Habecker, J. (2018) Pathology-Based Research in Africa. *Clinics in laboratory medicine*, **38**, 67–90.

Masamba, L.P.L., Jere, Y., Brown, E.R.S. & Gorman, D.R. (2016) Tuberculosis Diagnosis Delaying Treatment of Cancer: Experience From a New Oncology Unit in Blantyre, Malawi. *Journal of global oncology*, **2**, 26–29.

Milligan, M.G., Bigger, E., Abramson, J.S., Sohani, A.R., Zola, M., Kayembe, M.K.A., Medhin, H., Suneja, G., Lockman, S., Chabner, B.A. & Dryden-Peterson, S.L. (2018) Impact of HIV infection on the clinical presentation and survival of Non-Hodgkin lymphoma: a prospective observational study from Botswana. *Journal of global oncology*, **4**, 1–11.

Miranda-Filho, A., Piñeros, M., Znaor, A., Marcos-Gragera, R., Steliarova-Foucher, E. & Bray, F. (2019) Global patterns and trends in the incidence of non-Hodgkin lymphoma. *Cancer causes & control*, **30**, 489–499.

Montgomery, N.D., Liomba, N.G., Kampani, C., Krysiak, R., Stanley, C.C., Tomoka, T., Kamiza, S., Dhungel, B.M., Gopal, S. & Fedoriw, Y. (2016) Accurate real-time diagnosis of lymphoproliferative disorders in Malawi through clinicopathologic teleconferences. A model for pathology services in Sub-Saharan Africa. *American journal of clinical pathology*, **146**, 423–430.

Morton, L.M., Slager, S.L., Cerhan, J.R., Wang, S.S., Vajdic, C.M., Skibola, C.F., Bracci, P.M., de Sanjosé, S., Smedby, K.E., Chiu, B.C.H., Zhang, Y., Mbulaiteye, S.M., Monnereau, A., Turner, J.J., Clavel, J., Adami, H.-O., Chang, E.T., Glimelius, B., Hjalgrim, H., Melbye, M., Crosignani, P., Di Lollo, S., Miligi, L., Nanni, O., Ramazzotti, V., Rodella, S., Costantini, A.S., Stagnaro, E., Tumino, R., Vindigni, C., Vineis, P., Becker, N., Benavente, Y., Boffetta, P., Brennan, P., Cocco, P., Foretova, L., Maynadié, M., Nieters, A., Staines, A., Colt, J.S., Cozen, W., Davis, S., de Roos, A.J., Hartge, P., Rothman, N., Severson, R.K., Holly, E.A., Call, T.G., Feldman, A.L., Habermann, T.M., Liebow, M., Blair, A., Cantor, K.P., Kane, E.V., Lightfoot, T., Roman, E., Smith, A., Brooks-Wilson, A., Connors, J.M., Gascoyne, R.D., Spinelli, J.J., Armstrong, B.K., Kricker, A., Holford, T.R., Lan, Q., Zheng, T., Orsi, L., Dal Maso, L., Franceschi, S., La Vecchia, C., Negri, E., Serraino, D., Bernstein, L., Levine, A., Friedberg, J.W., Kelly, J.L., Berndt, S.I., Birmann, B.M., Clarke, C.A., Flowers, C.R., Foran, J.M., Kadin, M.E., Paltiel, O., Weisenburger, D.D., Linet, M.S. & Sampson, J.N. (2014) Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *Journal of the National Cancer Institute Monographs*, **2014**, 130–144.

Mwamba, P.M., Mwanda, W.O., Busakhala, N., Strother, R.M., Loehrer, P.J. & Remick, S.C. (2012) AIDS-related Non-Hodgkin's Lymphoma in Sub-Saharan Africa. Current status and realities of therapeutic approach. *Lymphoma*, **2012**.

Naresh, K.N., Raphael, M., Ayers, L., Hurwitz, N., Calbi, V., Rogena, E., Sayed, S., Sherman, O., Ibrahim, H.A.H., Lazzi, S., Mourmouras, V., Rince, P., Githanga, J., Byakika, B., Moshi, E., Durosinmi, M., Olasode, B.J., Oluwasola, O.A., Akang, E.E., Akenòva, Y., Adde, M., Magrath, I. & Leoncini, L. (2011) Lymphomas in sub-Saharan Africa–what can we learn and how can we help in improving diagnosis, managing patients and fostering translational research? *British journal of haematology*, **154**, 696–703.

National AIDS and STI Control Programme (NASCOP) (2012) Kenya AIDS Indicator Survey 2012. Adult Data Sheet - Population Reference Bureau. https://www.prb.org/kenya-aids-indicator-survey-adult-data/, 17 Jul 2019.

Ogwang, M.D., Zhao, W., Ayers, L.W. & Mbulaiteye, S.M. (2011) Accuracy of Burkitt lymphoma diagnosis in constrained pathology settings: importance to epidemiology. *Archives of Pathology & Laboratory Medicine*, **135**, 445–450.

Painschab, M.S., Kasonkanji, E., Zuze, T., Kaimila, B., Tomoka, T., Nyasosela, R., Nyirenda, R., Dhungel, B.M., Mulenga, M., Chikasema, M.,

Tewete, B., Mtangwanika, A., Chiyoyola, S., Mhango, W., Chimzimu, F., Kampani, C., Krysiak, R., Shea, T.C., Montgomery, N.D., Fedoriw, Y. & Gopal, S. (2019) Mature outcomes and prognostic indices in diffuse large B-cell lymphoma in Malawi: a prospective cohort. *British journal of haematology*, **184**, 364–372.

Parkin, D.M. & Liu, B. (2019) African Cancer Registry Network. https://afcrn.org/, 6 Sep 2019.

Parkin, D.M., Nambooze, S., Wabwire-Mangen, F. & Wabinga, H.R. (2010) Changing cancer incidence in Kampala, Uganda, 1991–2006. *International journal of cancer*, **126**, 1187–1195.

Parkin, D.M., Ferlay, J., Jemal, A., Borok, M., Manraj, S.S.N'da G.G., Ogunbiyi, F.J., Liu, B. & Bray F. (eds.) (2018) Cancer in Sub-Saharan Africa. International Agency for Research on Cancer, Lyon.

Parkin, D.M., Hämmerl, L., Ferlay, J. & Kantelhardt, E.J. (2019) Cancer in Africa 2018: the role of infections. *International journal of cancer*.

Patel, M., Philip, V., Omar, T., Turton, D., Candy, G., Lakha, A. & Pather, S. (2015) The impact of Human Immunodeficiency Virus infection (HIV) on lymphoma in South Africa. *Journal of Cancer Therapy*, **06**, 527–535.

Péko, J.-F. (2019) Scarcity of pathologists in the Republic of the Congo., Congo-Brazzaville.

Perry, A.M., Diebold, J., Nathwani, B.N., MacLennan, K.A., Müller-Hermelink, H.K., Bast, M., Boilesen, E., Armitage, J.O. & Weisenburger, D.D. (2016a) Non-Hodgkin lymphoma in the developing world: review of 4539 cases from the International Non-Hodgkin Lymphoma Classification Project. *Haematologica*, **101**, 1244–1250.

Perry, A.M., Perner, Y., Diebold, J., Nathwani, B.N., MacLennan, K.A., Müller-Hermelink, H.K., Bast, M., Boilesen, E., Armitage, J.O. & Weisenburger, D.D. (2016b) Non-Hodgkin lymphoma in Southern Africa: Review of 487 cases from The International Non-Hodgkin Lymphoma Classification Project. *British journal of haematology*, **172**, 716–723.

Re, A., Cattaneo, C. & Rossi, G. (2019) HIV and Lymphoma. From Epidemiology to Clinical Management. *Mediterranean Journal of Hematology and Infectious Diseases*, **11**, e2019004.

Rosenberg, S.A. (1982) National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. *Cancer*, 2112–2135.

Schonfeld, S.J., Erdmann, F., Wiggill, T., Singh, E., Kellett, P., Babb, C. & Schuz, J. (2016) Hematologic malignancies in South Africa 2000–2006. Analysis of data reported to the National Cancer Registry. *Cancer medicine*, **5**, 728–738.

Shiels, M.S. & Engels, E.A. (2012) Increased risk of histologically-defined cancer subtypes in HIV-infected individuals: clues for possible immunosuppression-related or infectious etiology. *Cancer*, **118**, 4869–4876.

Swerdlow, S.H., Campo, E., Pileri, S.A., Harris, N.L., Stein, H., Siebert, R., Advani, R., Ghielmini, M., Salles, G.A., Zelenetz, A.D. & Jaffe, E.S. (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*, **127**, 2375–2390.

The Demographic and Health Surveys (DHS) Program (2019) DHS data sets. https://dhsprogram.com/data/, 17 Jul 2019.

Thorley-Lawson, D., Deitsch, K.W., Duca, K.A. & Torgbor, C. (2016) The Link between Plasmodium falciparum Malaria and Endemic Burkitt's Lymphoma—New Insight into a 50-Year-Old Enigma. *PLoS Path*, **12**, e1005331.

United Nations Joint Programme on HIV/AIDS (UNAIDS) (2018) UNAIDS data 2018. https://www.unaids.org/en/resources/documents/2018/unaids-data-2018, 15 Jun 2019.

Vannata, B. & Zucca, E. (2015) Primary extranodal B-cell lymphoma. Current concepts and treatment strategies. *Chinese clinical oncology*, **4**, 10.

Vockerodt, M., Yap, L.-F., Shannon-Lowe, C., Curley, H., Wei, W., Vrzalikova, K. & Murray, P.G. (2015) The Epstein-Barr virus and the pathogenesis of lymphoma. *The Journal of pathology*, **235**, 312–322.

Wiggill, T.M., Mantina, H., Willem, P., Perner, Y. & Stevens, W.S. (2011) Changing pattern of lymphoma subgroups at a tertiary academic complex in a high-prevalence HIV setting. A South African perspective. *Journal of acquired immune deficiency syndromes*, **56**, 460–466.

Wiggill, T.M., Mayne, E.S. & Willem, P. (2013) Challenges in lymphoma diagnosis in HIV positive patients in the South African setting. *Transfusion and Apheresis Science*, **49**, 157–162.

Wilkins, B.S. (2011) Pitfalls in lymphoma pathology: avoiding errors in diagnosis of lymphoid tissues. *Journal of clinical pathology*, **64**, 466–476.

Zelenetz, A.D., Gordon, L.I., Abramson, J.S., Advani, R., Bartlett, N.L., Caimi, P.F., Chang, J.E. & Chavez, J.C. (2019) NCCN harmonized guidelines for Sub-Saharan Africa. *B-Cell lymphoma*. https://www.nccn.org/harmonized/default.aspx, 5 Sep 2019.

Zucca, E., Bertoni, F., Vannata, B. & Cavalli, F. (2014) Emerging role of infectious etiologies in the pathogenesis of marginal zone B-cell lymphomas. *Clinical cancer research*, **20**, 5207–5216.

The Oncologist, 2023, **XX**, 1–14
https://doi.org/10.1093/oncolo/oyad157
Advance access publication 27 June 2023
Original Article

Guideline Concordance of Treatment and Outcomes Among Adult Non-Hodgkin Lymphoma Patients in Sub-Saharan Africa: A Multinational, Population-Based Cohort

Nikolaus Christian Simon Mezger[1], Lucia Hämmerl[1], Mirko Griesel[1], Tobias Paul Seraphin[1], Yvonne Walburga Joko-Fru[2,3], Jana Feuchtner[1], Annelle Zietsman[2,4], Jean-Félix Péko[2,5], Fisihatsion Tadesse[2,6], Nathan Gyabi Buziba[2,7], Henry Wabinga[2,8], Mary Nyanchama[2,9], Eric Chokunonga[2,10], Mamadou Kéita[2,11,12], Guy N'da[2,13], Cesaltina Ferreira Lorenzoni[2,14,15], Marie-Thérèse Akele-Akpo[2,16], Jörg Michael Mezger[17], Mascha Binder[18], Biying Liu[2], Marcus Bauer[19], Oliver Henke[20], Ahmedin Jemal[21], Eva Johanna Kantelhardt*[,1,22]

[1]Global Health Working Group, Institute of Medical Epidemiology, Biometrics and Informatics, Martin-Luther-University Halle-Wittenberg, Halle, Germany
[2]African Cancer Registry Network, Oxford, UK
[3]Nuffield Department of Population Health, University of Oxford, Oxford, UK
[4]Dr AB May Cancer Care Centre, Windhoek, Namibia
[5]Registre des cancers de Brazzaville, Brazzaville, Republic of the Congo
[6]Division of Hematology, Department of Internal Medicine, University and Black Lion Hospital, Addis Ababa, Ethiopia
[7]Eldoret Cancer Registry, School of Medicine, Moi University, Eldoret, Kenya
[8]Kampala Cancer Registry, Makerere University School of Medicine, Kampala, Uganda
[9]National Cancer Registry, Kenya Medical Research Institute, Nairobi, Kenya
[10]Zimbabwe National Cancer Registry, Harare, Zimbabwe
[11]Service du Laboratoire d'Anatomie et Cytologie Pathologique, Bamako, Mali
[12] CHU du point G , Bamako, Mali
[13]Registre des cancers d'Abidjan, Abidjan, Côte d'Ivoire
[14]Departamento de Patologia, Faculdade de Medicina, Universidade Eduardo Mondlane, Hospital Central de Maputo, Mozambique
[15]Registo de Cancro, Ministério da Saúde, Maputo, Mozambique
[16]Département d'anatomo-pathologie, Faculté des Sciences de la Santé, Cotonou, Benin
[17]Albert-Ludwig University of Freiburg, Germany
[18]Department of Internal Medicine IV, Oncology/Hematology, Martin-Luther-University Halle-Wittenberg, Halle, Germany
[19]Institute of Pathology, Martin-Luther-University Halle-Wittenberg, Halle, Germany
[20]Section Global Health, Institute for Public Health and Hygiene, University Hospital Bonn, Germany
[21]Surveillance and Health Equity Science, American Cancer Society, Atlanta, USA
[22]Department of Gynaecology, Martin-Luther-University Halle-Wittenberg, Halle, Germany

*Corresponding author: Eva Johanna Kantelhardt, MD, Institute of Medical Epidemiology, Biometrics and Informatics, Martin-Luther-University Halle-Wittenberg, Magdeburger Str 8, 06112 Halle (Saale), Germany. Email: eva.kantelhardt@uk-halle.de

Abstract

Background: Although non-Hodgkin lymphoma (NHL) is the 6th most common malignancy in Sub-Saharan Africa (SSA), little is known about its management and outcome. Herein, we examined treatment patterns and survival among NHL patients.

Methods: We obtained a random sample of adult patients diagnosed between 2011 and 2015 from 11 population-based cancer registries in 10 SSA countries. Descriptive statistics for lymphoma-directed therapy (LDT) and degree of concordance with National Comprehensive Cancer Network (NCCN) guidelines were calculated, and survival rates were estimated.

Findings: Of 516 patients included in the study, sub-classification was available for 42.1% (121 high-grade and 64 low-grade B-cell lymphoma, 15 T-cell lymphoma and 17 otherwise sub-classified NHL), whilst the remaining 57.9% were unclassified. Any LDT was identified for 195 of all patients (37.8%). NCCN guideline-recommended treatment was initiated in 21 patients. This corresponds to 4.1% of all 516 patients, and to 11.7% of 180 patients with sub-classified B-cell lymphoma and NCCN guidelines available. Deviations from guideline-recommended treatment were initiated in another 49 (9.5% of 516, 27.2% of 180). By registry, the proportion of all patients receiving guideline-concordant LDT ranged

Received: 5 August 2022; Accepted: 24 April 2023.

from 30.8% in Namibia to 0% in Maputo and Bamako. Concordance with treatment recommendations was not assessable in 75.1% of patients (records not traced (43.2%), traced but no sub-classification identified (27.8%), traced but no guidelines available (4.1%)). By registry, diagnostic work-up was in part importantly limited, thus impeding guideline evaluation significantly. Overall 1-year survival was 61.2% (95%CI 55.3%-67.1%). Poor ECOG performance status, advanced stage, less than 5 cycles and absence of chemo (immuno-) therapy were associated with unfavorable survival, while HIV status, age, and gender did not impact survival. In diffuse large B-cell lymphoma, initiation of guideline-concordant treatment was associated with favorable survival.

Interpretation: This study shows that a majority of NHL patients in SSA are untreated or undertreated, resulting in unfavorable survival. Investments in enhanced diagnostic services, provision of chemo(immuno-)therapy and supportive care will likely improve outcomes in the region.

Implications for Practice

Although advances in care have tremendously improved non-Hodgkin lymphoma (NHL) outcomes, disparities in uptake of treatment still confine survival across the globe. While NHL is a common disease in Sub-Saharan Africa, little is known about its treatment and survival. Our multinational, population-based study aimed to assess the current quality of care and survival in 10 countries. Patients across the region presented at late stages, with poor ECOG performance status, and lacked subtyping. Absence of any therapy was identified in some 3 in 5 patients, and non-guideline-concordant therapy in 6 of 7, with all factors associated with unfavorable survival. Our study shows that many NHL patients are unable to access high-quality diagnostic and treatment services, providing a baseline for targeted investments. With regard to clinical practice, we underline the importance of NHL grading and subtyping, patient-centered treatment mindful of possible side effects, and relevance of therapy completion.

Introduction

Non-Hodgkin lymphoma (NHL) is the 6th most common type of malignant neoplasia in Sub-Saharan Africa (SSA).[1,2] Incidence is continuously rising and by 2040 the number of new cases per year is expected to nearly double to more than 60 000.[3-5] Many subtypes of NHL are treatable with good outcomes, with a 5-year survival rate of 73.2% for patients in the United States.[6] In SSA, however, resources for cancer care are limited.[7-10] Therefore, the National Comprehensive Cancer Network (NCCN) developed Harmonized Guidelines on a variety of B-cell lymphoma subtypes for resource-stratified use in the region.[11] In this context, identification of NHL subtype is crucial for specific therapy, however, a high frequency of unclassified lymphoma has been reported across the region.[8-10]

Previous studies on NHL treatment patterns in SSA were hospital-based studies, with high proportion of late-stage and aggressive diseases,[8,10,12-16] limited treatment options, and poor survival.[10,17-22] The aim of our study was to assess the application of NHL treatment according to NCCN harmonized guidelines in this region and to identify factors influencing survival using a multi-national, real-world cohort within the African Cancer Registry Network (AFCRN, https://afcrn.org).

Methods

Study Setting

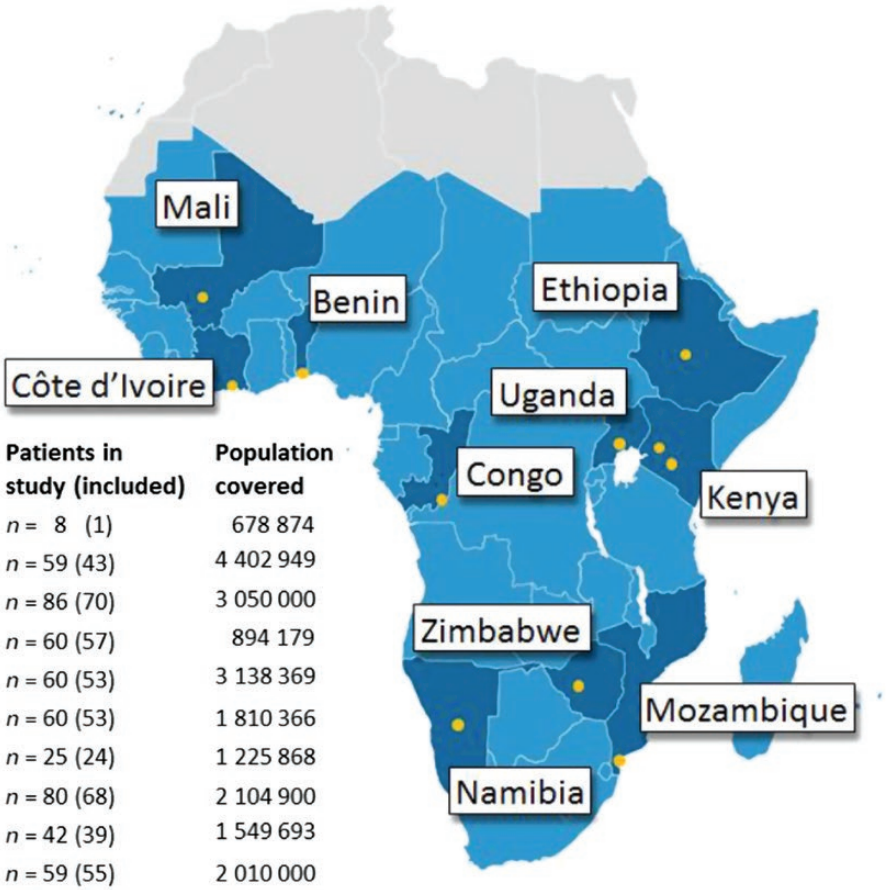
In 2014, AFCRN coordinated 23 regional population-based cancer registries (PBCRs) as International Agency for Research on Cancer's regional hub in SSA.[23] Of these, 11 registries in 10 countries consented to serve as study centers, covering a population of roughly 21.5 million (Fig. 1). We included NHL patients aged 15 and above with B-cell and T-cell lymphoma as well as unclassified lymphoma (International Classification of Diseases-10 codes C82–C96 and C96) and diagnosed between 2011 and 2015. Hodgkin lymphoma and pediatric lymphoma aged 14 and below were not included. Power was calculated for the entire cohort but not for individual sites: A minimal sample size of 404 patients produces a 2-sided 95% CI with a width equal to 0.1 when the sample proportion of patients with adequate care is 0.500. We assumed a drop-out rate of 33% and therefore aimed for 600 patients. Of 1068 patients available, a study population of 599 patients (56.1%) was thus selected at random.

Data Collection

As previously described in detail, registry staff continuously retrieve information on demographics, diagnosis including NHL subtype, and vital status from hospital records.[24] Occasionally, data on treatment modalities (eg, chemotherapy yes/no) are collected. To complement PBCR routine data, clinical records were re-evaluated to collect information on patterns of care. Lymphoma morphology registered was verified and amended by assessing pathology reports, and, in the absence of definitive pathological diagnoses, those noted in clinical records were used.[24] Stage was assessed in line with Lugano and Binet classifications.[26,27] When the stage had not been assigned in records, it was considered less advanced if no suggestion of disseminated nodal or extranodal involvement was found. Vital status was assessed by follow-up calls. Patients were considered "traced" if information beyond PBCR data (eg, detailed information on clinical diagnostics (such as ECOG performance status (PS) or HIV status) and/or lymphoma-directed treatment (such as chemotherapy regimen administered or radiotherapy) and/or survival status) was obtained from hospital records and/or follow-up calls. Patients were considered "not traced" if no information beyond PBCR data were available. Follow-up was open for 7 years until April 31, 2018.

Therapy Evaluation

For NHL subtypes with NCCN Harmonized Guidelines for SSA[11] available, we established an evaluation scheme assessing completion of first-line therapy and adherence to guidelines. For therapy evaluation, patients were allocated to 3 groups: sub-classified NHL with guidelines available, sub-classified NHL without guidelines available, and unclassified NHL. NCCN Harmonized Guidelines for SSA were available for diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia/small lymphocytic lymphoma



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

Figure 1. Map of Sub-Saharan Africa.[24,25] Countries and cities of participating population-based cancer registries are highlighted. On the left, the numbers included in the random sample are shown along with the covered population in the registry area. For details see also Supplementary Table S2.

(CLL/SLL), Burkitt (BL), follicular (FL), marginal zone, and lymphoplasmacytic lymphoma. For these subtypes, "guideline concordance" was defined as NCCN's harmonized "generally available standard of care." "Deviation from guidelines" was defined, again according to NCCN, as "regional options that may be considered when availability precludes standard of care." Non-guideline concordant lymphoma-directed therapy (LDT) was defined "any other therapy." As an example, for DLBCL, NCCN recommends rituximab (R) + cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP). Deviation from guidelines in DLBCL was thus defined as CHOP without rituximab. Other chemotherapy regimens were labeled as any other therapy. Concerning guideline-concordant therapy *completion* for DLBCL, at least 5 cycles of RCHOP or 3 cycles of RCHOP + radiotherapy in stage I or II were necessary for therapy to be considered complete. For completion of guideline-deviating therapy in DLBCL, the same number of cycles for CHOP was necessary. Concerning guideline concordance of treatment for indolent NHL, NCCN guidelines allow for a variety of chemo(immuno-)therapeutic agents. However, due to the heterogeneous nature of eg, CLL/SLL and FL, NCCN does not specify a minimum number of cycles. Thus, any number of cycles of chemo(immuno-)therapy was accepted regarding the completeness of guideline-concordant therapy (for details on therapy evaluation see Supplementary Table S1). Patients with clinical records traced, but without any information on LDT were labeled as "no therapy." For presentation of therapy evaluation, patients not traced without PBCR information on LDT were grouped separately. Both for subtypes without guidelines available and for unclassified NHL, application of guidelines was not feasible. We differentiated between polychemo(immuno-)therapy (PCT) vs. "any other therapy" vs. "no therapy," considering sole radiotherapy without chemo(immuno-)therapy as "any other therapy." Similarly, we labeled sole splenectomy and other operations in stage I lymphoma as "any other therapy," but regarded all other operations as supportive care and therefore defined these as "no therapy."

Statistical Analysis

For statistical analysis, IBM SPSS Statistics (version 25) was used. For longitudinal data, Kaplan-Meier's method and multivariable Cox proportional hazard model were used. First, we assessed for the condition of "missing at random" (uninformative censoring) by performing reverse Kaplan-Meier's analysis. We then restricted the analysis to patients with the survival of at least 1 month to allow time for initiation of therapy and to account for bias from missing treatment through early death. Kaplan-Meier's method accounted for further loss to follow up. For survival analysis, we grouped patients traced without indication of LDT and patients not traced, assuming that patients not traced despite our efforts did not receive any LDT. We estimated simple and multivariable hazard

ratios (HR), and computed 1- to 3-year age-standardized overall survival using the "popEpi" package for R software, while adopting Corazziari et al's ICSS 1 age standard.[28]

Ethical Consideration

The study protocol was approved by the AFCRN research committee (March 2, 2016) and the Martin-Luther-University, Halle Ethical Review Board, and it was in line with the Declaration of Helsinki. Anonymized secondary data were collected from each participating registry under existing regulations and national laws of the respective registries.

Role of the Funding Source

Funders had no role in study design, collection analysis, and interpretation of data, in writing of the report, and in decision to submit the paper for publication.

Results

Of 599 patients, 516 patients were included (Fig. 2). A total of 83 patients had to be excluded due to duplicates, other diagnoses, recurrence, or not meeting the age inclusion criteria. Additional information, eg, on treatment and/or survival was obtained for 293 patients ("traced," 56.8%, Supplementary Table S2).

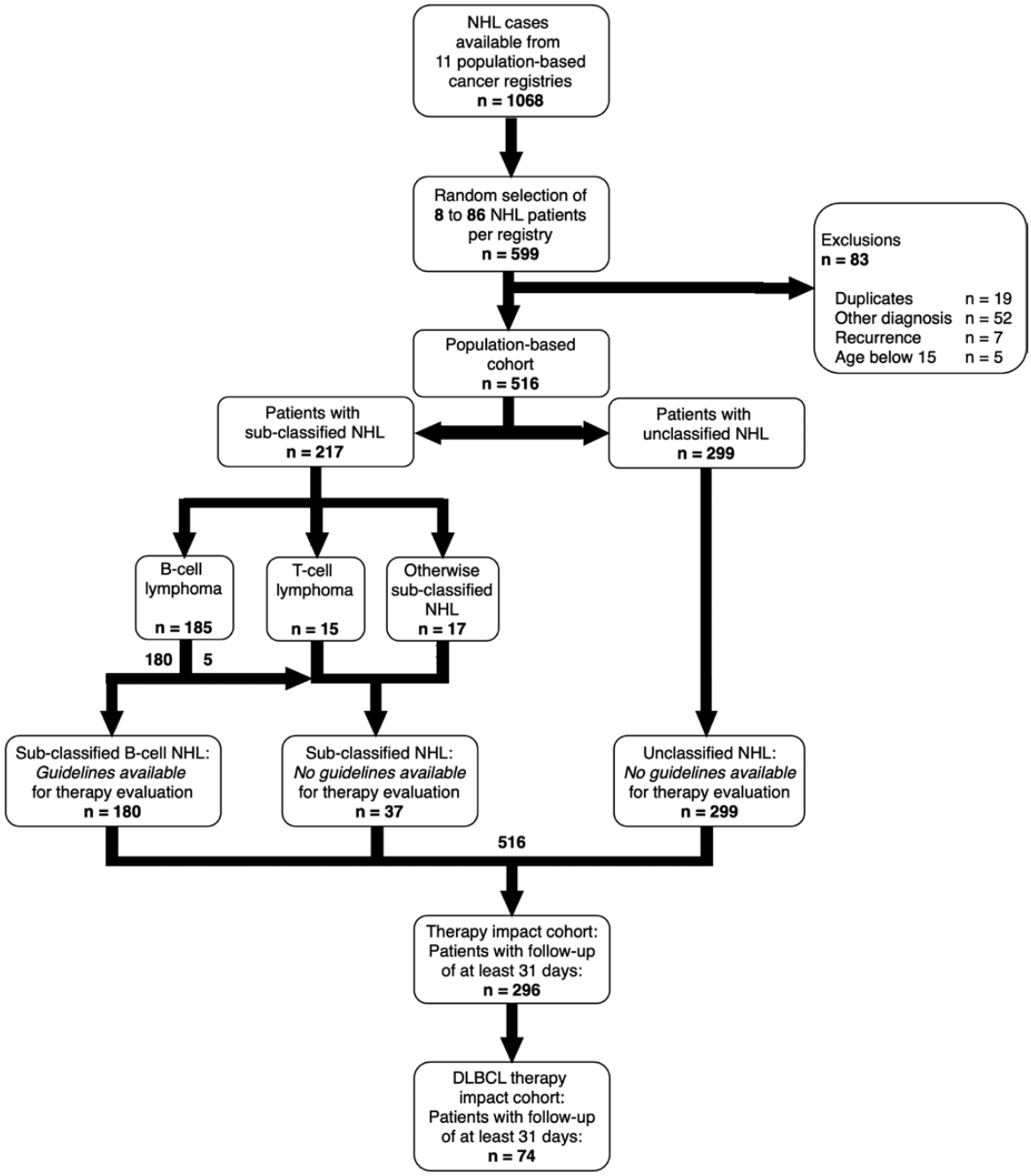


Figure 2. Flow chart of the study population. NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma.

Baseline and Diagnostic Characteristics

Patient characteristics have been published elsewhere in detail.[24] Median age was 45 years and 43.4% of patients were female. ECOG PS of 2 or worse was documented in 61.4%, and 79.3% presented with B symptoms. Advanced stage, defined as Lugano stages III and IV and as Binet C for CLL/SLL, was diagnosed in 73.0%. Of 154 tested patients, 63.0% were HIV positive (Supplementary Table S3). In 85.3% combined antiretroviral therapy had been initiated prior to diagnosis of NHL. Sub-classification was documented in 217 patients (42.1) while 299 NHL (57.9%) remained unclassified. By registry, proportion of sub-classified NHL ranged from 94.1% in Namibia to 8.3% in Maputo.[24] Of all sub-classified lymphoma, 121 were high-grade (55.8%) and 64 low-grade B-cell lymphoma (29.5%), 15 T-cell lymphoma (6.9%), and 17 otherwise sub-classified NHL (7.8%) (Supplementary Table S4).

Therapy

Any systemic therapy was documented in 187 of all 516 patients (36.2%). For these, first-line chemo(immuno-)therapy consisted of CHOP (-related) and cyclophosphamide, vincristine, and prednisone (COP) (-related) protocols in 62.0% and 10.7%, respectively. Rituximab was the only immunotherapy agent identified and administered in 20 of 187 (10.7%). Patients received a median of 6 cycles of first-line systemic therapy (interquartile range: 3–6 cycles). Among all 83 patients receiving a minimum of 6 cycles of systemic therapy, 49 had sub-classified NHL and 34 unclassified NHL. Overall, 2 patients received second-line systemic therapy. Of the 195 patients with any LDT initiated (37.8%), radiotherapy was identified in 34 cases, and lymphoma-directed surgery in 28 (Table 1). For details, see Supplementary Table S5.

Guideline Concordance

Of all 516 patients, 180 patients with sub-classified NHL and guidelines available were eligible for therapy evaluation. Namely, patients diagnosed with DLBCL (48.8% of all 217 sub-classified NHL), CLL/SLL (18.8%), BL (6.0%), FL (5.5%), marginal zone (3.2%), and lymphoplasmacytic lymphoma (1.0%) were evaluated with respect to concordance with the NCCN guidelines harmonized for SSA.[11] Of these 180 cases, we found both initiation and completion of guideline-recommended treatment for 21 patients (11.7%) (Fig. 3A and 3B). Initiation of guideline-deviating therapy was found for another 49 (27.2%), of which 35 (19.4%) managed to complete respective therapies. No therapy could be identified for 86 of 180 cases (47.8%, including patients not traced). For the remaining 37 patients with sub-classified NHL, predominantly T-cell and otherwise sub-classified NHL, no harmonized guidelines were available. Further, no guidelines were available for the 299 patients with unclassified NHL.

Disparities Within and Between Registries

Within and between the PBCR cohorts, we found huge disparities in therapy initiation, ranging from patients without any treatment to patients treated in concordance with guidelines. For example, 11.6% of patients in Abidjan initiated guideline-concordant therapy or a deviation thereof, while in 72.1% no treatment was documented. Similarly, in Bamako and Brazzaville only 15.4% and 12.8% had any treatment documented, respectively (Fig. 4A). The largest proportion of patients with any treatment initiated was found in Nairobi (71.7%) followed by Addis Ababa (57.1%). In Namibia, the largest proportion of patients completed therapy concordantly with guidelines (30.8%), for Maputo and Bamako, none were treated in concordance with guidelines—with only 11 sub-classified NHL cases in Bamako (20.8%) and 2 cases in Maputo (8.3%) (Fig. 4B). Radiotherapy was identified in patients from 4 registries only, Addis Ababa, Kampala, Nairobi, and Namibia.

Survival

Any follow-up information was available for 384 patients. For all patients, median follow-up and survival were 6 and 20 months, respectively. Observed 1- and 3-year overall survival (OS) was 61.2% (95% CI, 55.3%-67.1%) and 37.2% (30.5%-43.9%) (Fig. 5A), respectively, varying substantially between the different PBCR areas: 1-year-OS was highest for patients in Addis Ababa (76.3%) and worst for patients in Bulawayo (37.5%) (Supplementary Table S6). The 1-and 3-year age-standardized overall survival was 62.3% (95%CI, 52.9%-70.4%) and 32.9% (22.1%-44.2%), respectively. As for median survival of subtypes, we found 48 months in DLBCL (n = 110), 29 months in CLL/SLL (n = 40), 8 months in BL (n = 13), 9 months in FL (n = 12), and 15 months in unclassified lymphoma (Fig. 5B). Differences in survival with respect to any therapy initiation in all NHL were rather small (Fig. 5C), but better survival was found in patients completing at least 5 cycles of chemo(immuno-)therapy (Fig. 5D). In DLBCL, both any therapy initiation as well as completion of guideline-recommended treatment were associated with better survival (Fig. 5E and 5F). Kaplan-Meier estimates for clinical characteristics and further association of guideline-concordant treatment with improved survival are shown in Supplementary Fig. S1.

Factors Associated With Outcome

In unadjusted Cox proportional hazards modeling, mortality of the cohort (follow-up at least 30 days, n = 296) was associated with ECOG PS, presence of B symptoms, missing assessment of B symptoms, advanced or missing stage, and somewhat associated with lack of subtype. Mortality was also associated with receipt of less than 5 cycles of any chemo(immuno-)therapy and lack of treatment. For DLBCL (n = 74), we found mortality associated with age of 60 and older, absent staging, and lack of guideline-concordant therapy or absence of any therapy. Notably, for neither cohort HIV status was associated with mortality (Supplementary Table S7).

In adjusted Cox proportional hazards modeling controlling for selected parameters in all NHL patients, worse survival remained (somewhat) associated with worse ECOG PS, advanced stage, B symptoms, less than 5 cycles of any chemo(immuno-)therapy, and absence of any therapy (Fig. 6A). For DLBCL patients only, absent staging and initiation of therapy other than guideline-recommended and absence of any therapy remained (somewhat) associated with worse survival in multivariate Cox regression (Fig. 6B).

Reverse Kaplan-Meier analysis suggested that in all NHL patients as well as in the DLBCL cohort, some covariates had a similar pattern of censoring over time: for sex, site involved, and HIV status, censoring appeared at random. NHL patients

Table 1. Treatment modalities in the population-based cohort (*n* = 516).

Chemo(immuno-)therapy regimen	Patients (*n*)	% of all receiving systemic therapy	Cycles applied	Patients (*n*)	% of therapy evaluation cohort	Cycles applied, median
CHOP and similar	116	62	5 or more	71	38	6
			4 or less	34	18.2	2
			Unknown # of cycles	11	5.9	n/a
COP and similar	20	10.7	5 or more	10	5.3	6
			4 or less	9	4.8	2
			Unknown # of cycles	1	0.5	n/a
Other polychemo(immuno-)therapy regimen	8	4.3	5 or more	3	1.6	7
			4 or less	5	2.7	3
Monotherapy	15	8	5 or more	3	1.6	6
			4 or less	5	2.7	4
			Unknown # of cycles	7	3.7	n/a
Unknown regimen	28	15	5 or more	5	2.7	6
			4 or less	2	1.1	3
			Unknown # of cycles	21	11.2	n/a
Any systemic therapy	187	100	5 or more	92	49.2	6
			4 or less	55	29.4	2
			Unknown # of cycles	40	21.4	n/a
Radiotherapy dose applied		% of all receiving radiotherapy				
Thirty gray or more	17	48.1				
Less than 30 gray	7	22.2				
Unknown dose	10	29.6				
Any radiotherapy	34	100				
Surgery type		% of all receiving surgery				
Splenectomy and stage I lymphnode resection	5	17.9				
Other surgery (diagnostic/palliative/unspecified)	23	82.1				
Any lymphoma-directed surgery (including diagnostic surgery, excluding biopsies)	28	100				
Any lymphoma-directed therapy	195	37.8 (of population-based cohort, n = 516				

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; COP, cyclophosphamide, vincristine, prednisone.

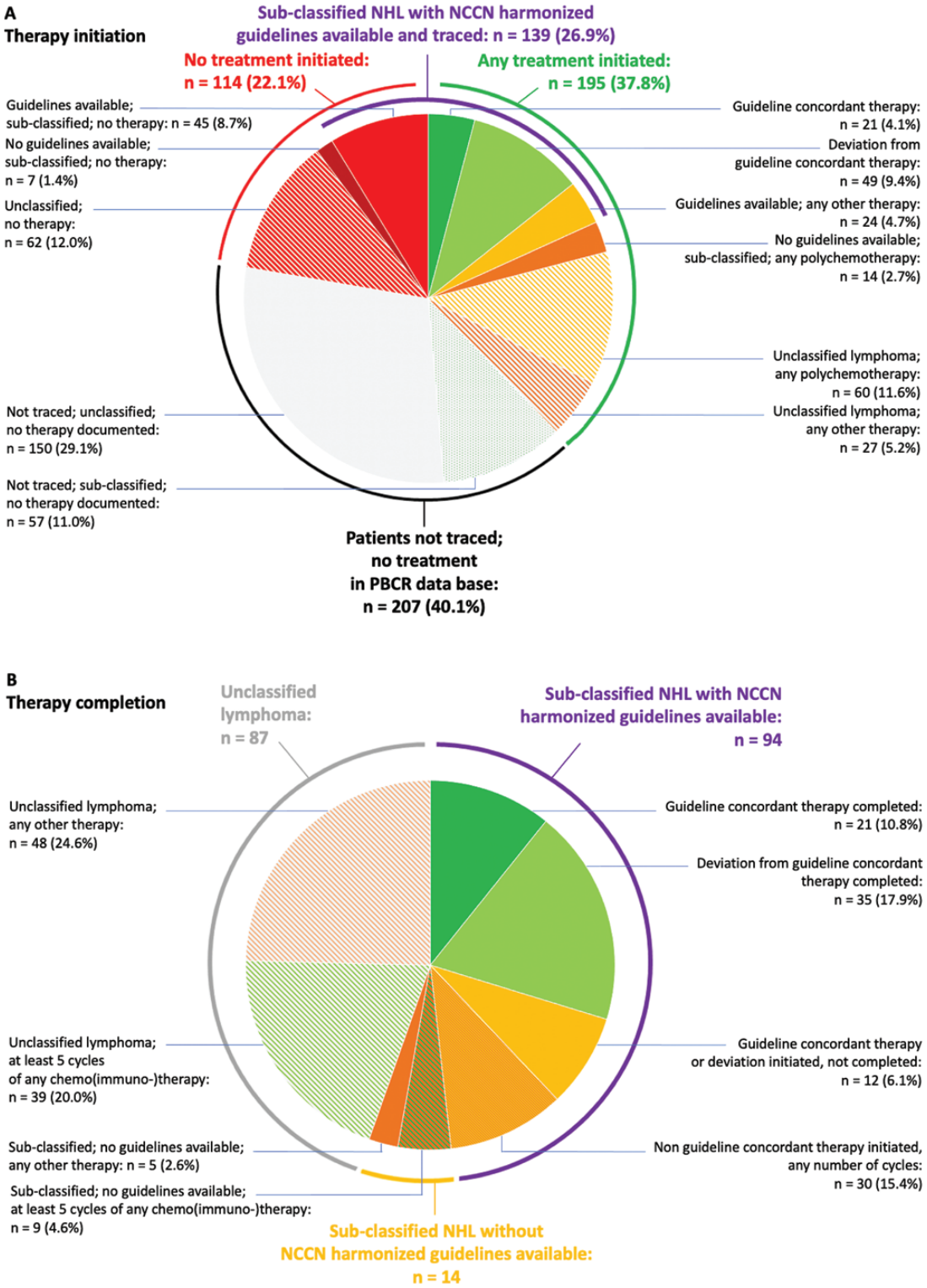


Figure 3. Evaluation of guideline concordance. (**A**) Depicts evaluation of therapy *initiation* in the population-based cohort (*n* = 516). Percentages refer to the proportion of all patients in cohort. (**B**) Depicts evaluation of therapy *completion* in all patients with any treatment documented (*n* = 195 (37.8% of total cohort)). The groups marked in green depict patients completing at least 5 cycles of chemo(immuno-)therapy. Percentages refer to proportion of all patients with any treatment documented. Evaluation refers to "therapy evaluation scheme" in Supplementary Table S1. PBCR, population-based cancer registry.

with ECOG PS of 1 or better versus others, early-stage versus others, lack of B symptoms, sub-classified NHL as well as completion of at least 5 cycles of any chemotherapy versus others, had less censoring. For DLBCL patients, ECOG PS of 1 or better, any staging, and initiation of guideline-concordant therapy equally had less censoring.

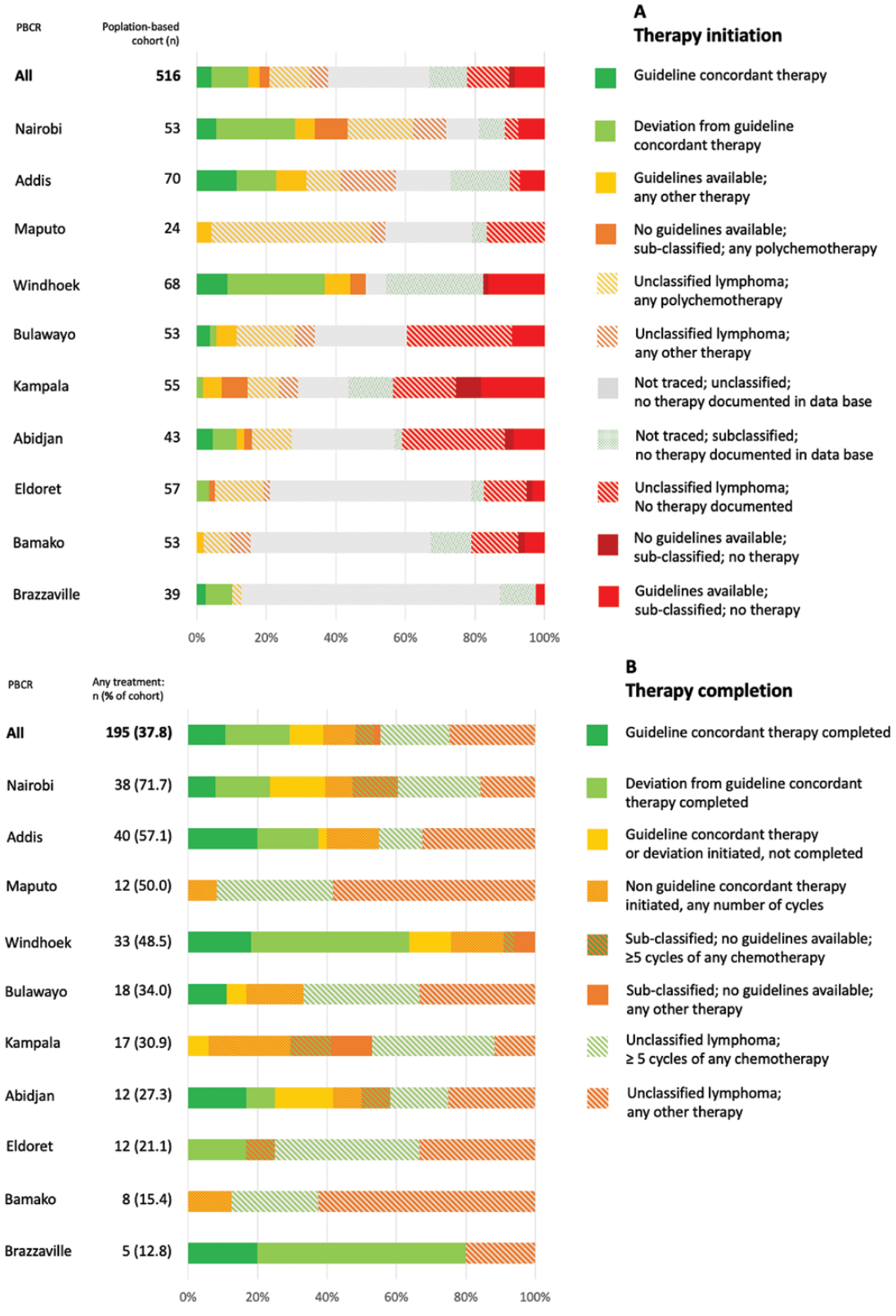


Figure 4. Stratification of evaluation of guideline concordance by population-based cancer registries. (**A**) Depicts evaluation of therapy *initiation* within the population-based cohort (n = 516). Percentages refer to proportion of all patients in respective population-based cancer registries. (**B**) Depicts evaluation of therapy *completion* among all patients with any treatment documented (n = 195 (37.8% of total cohort)). Percentages refer to proportion of all patients with any treatment documented in respective population-based cancer registries. Evaluation refers to "Therapy evaluation scheme" in Supplementary Table S1. Cotonou was excluded from figure due to small patient number (n = 1). PBCR, population-based cancer registry.

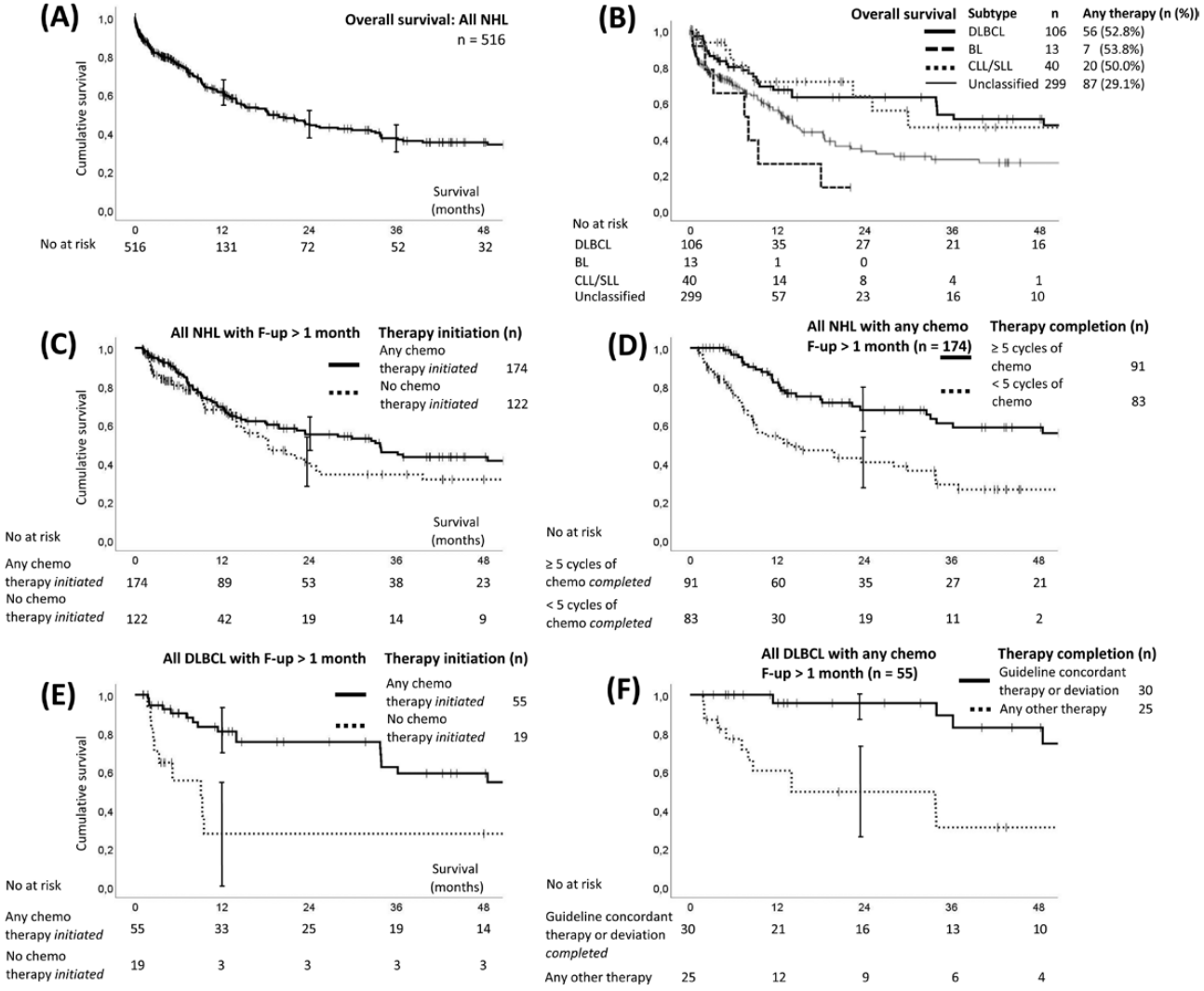


Figure 5. Survival by Kaplan-Meier estimates. (**A**) Overall survival of population-based cohort (n = 516); 95% CI indicated for 12, 24, and 36 months. (**B**) Overall survival of population-based cohort stratified by different subtypes and unclassified lymphoma. (**C**) Survival of population-based cohort with at least 1 month of survival (n = 296) with respect to therapy initiation and (**D**) those surviving at least 1 month that initiated any chemotherapy (n = 174), with respect to completion of chemo(immuno-)therapy cycles. (**E**) Survival of DLBCL with at least 1 month of survival (n = 74) with respect to therapy initiation and (**F**) DLBCL patients surviving at least 1 month that received any chemo(immuno-)therapy (n = 55) with respect to therapy completion concording with NCCN guidelines harmonized for Sub-Saharan Africa. No, Number; DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; F-up, follow-up.

Discussion

This study represents, to our knowledge, the first population-based multinational investigation on treatment and survival in adult non-Hodgkin lymphoma patients in Sub-Saharan Africa. Our objective was to evaluate guideline-concordance of therapy and survival in real-world patients. The main results of our study were: (1) The proportion of patients treated was low and guideline-concordant therapy was initiated in very few patients. (2) Survival of our study population was poor, while guideline-concordant treatment was associated with improved outcomes. (3) Treatment and survival of NHL patients varied considerably within and between the population-based cancer registries included.

(1) A concerning finding is the small share of NHL patients that received guideline-concordant care. Roughly summarized, NCCN Harmonized Guidelines for SSA recommend intensified chemotherapy regimen plus rituximab for the predominant aggressive subtypes such as DLBCL and BL as well as for advanced FL and MZL, and monotherapy for CLL/SLL.[11] However, only 13.1% of patients in our population-based cohort initiated guideline-concordant treatment or therapy with some deviation. As reported previously by our group in detail, one important factor attributing to this strikingly low proportion is the absence of sub-classification in more than half of patients (57.9%) and hence failure to apply guideline-concordant therapy.[24] Our results stress the importance of diagnostic work-up in NHL. Uniform treatment approaches disregarding subtype of lymphoma appear common in the region, eg, administration of oral polychemotherapy or (R-)CHOP for any NHL.[10,22,29] Only in recent years, multiple hospital-based studies have shed more light on feasibility of grade- and subtype-directed treatment approaches in SSA, eg, on AIDS-related DLBCL,[30] aggressive B- and T-cell lymphoma,[20] BL,[18] and HIV-associated aggressive NHL.[31] We suggest that in case of further amendment of NCCN Harmonized Guidelines, recommendations for treatment of

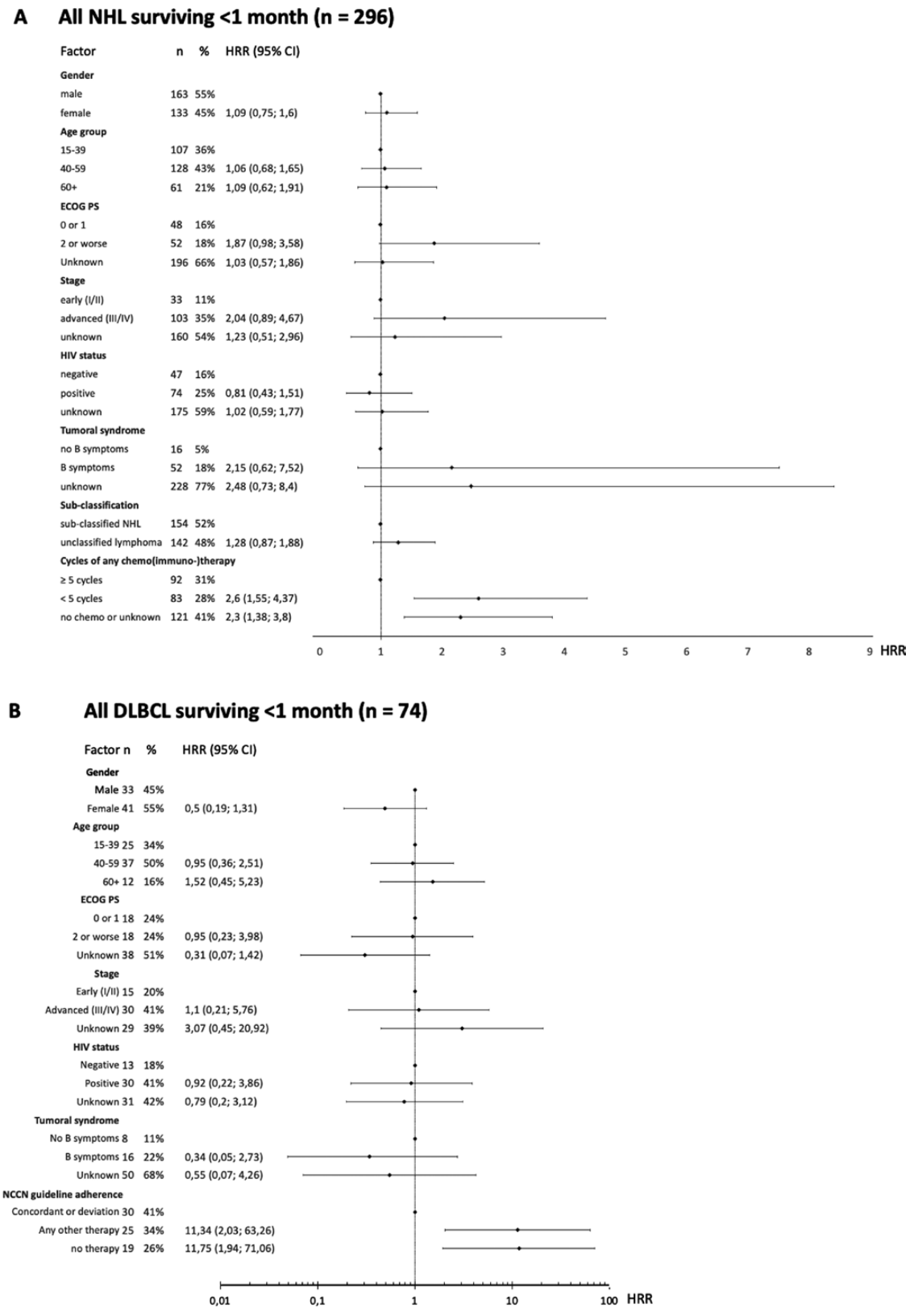


Figure 6. Results of multivariable Cox regression analysis for risk of early death. **A:** All NHL in the population-based cohort with at least 1 month of survival (n = 296). **B:** All DLBCL in the population-based cohort with at least 1 month of survival (n = 74). HRR, hazard rate ratio.

high- and low-grade lymphoma may be considered when further subtyping is not feasible.Another reason may be the lack of certain treatments even when sub-classification of NHL is available. Almost all patients in our cohort received CHOP- (73.0%) or COP-based (12.6%) regimens. An important factor contributing to absence of differentiated treatment may be cost and availability of chemotherapy agents (eg, highly effective bendamustine for MZL and CLL/

SLL[11]). In high-income countries, the introduction of rituximab has led to unprecedented rates of long-term cure and control of B-cell lymphoma.[32,33] CD20 antibodies are included in NCCN Harmonized Guidelines for several B-cell lymphoma subtypes,[11] and cost of biosimilars tends to be lower than rituximab.[7] However, they seemed hardly available in most SSA settings at the time[7,22] though recently proven safe, efficient,[17] and cost-effective for Malawi.[34] In our cohort, the majority of the 20 patients receiving rituximab came from Namibia, a middle-income country where public health insurance started covering the drug in 2013. To improve evidence-based treatment for predominantly aggressive lymphoma of B-cell lineage in SSA, health systems across SSA should increase efforts to procure and provide a wider range of systemic therapy agents at low cost, first and foremost rituximab or its biosimilars. Inclusion of not least CD20 antibodies in universal health coverage could leverage provision of adequate care for patients in the region. A fourth reason for low proportion of guideline-concordant care is the lack of NCCN Harmonized Guidelines for T-cell NHL and other rare entities such as plasmablastic and mantle cell lymphoma (17.1% of all sub-classified NHL).[11] More importantly, fifth, no treatment was documented in 114 of 297 patients traced (39.4%), and despite thorough investigation, another 217 of the 516 patients could not be traced (42.1%). In a worst-case scenario, where all untraced patients received no therapy, the share of patients without any lymphoma-directed treatment would amount to 62.2%.

(2) Overall survival in our study was poor (61.2% one-year survival), but slightly higher than outcomes reported by hospital-based and single-centered studies.[10,20,21,31] We believe that this difference is mostly explained by the high proportion of patients with poor health status and without any treatment documented who were lost to follow up early and therefore censored in analysis.Initiation of guideline-concordant treatment was associated with improved survival for sub-classified NHL. For DLBCL, the most frequent NHL subtype in our cohort, the largest impact on survival of all variables studied was found for administration of at least 5 cycles of (R-)CHOP. In our study, DLBCL patients receiving CD20 antibodies in addition to CHOP appeared to have improved survival, but due to low patient numbers these findings were not statistically significant in our population-based setting. Findings from Malawi indicate that treatment including rituximab is feasible and cost-effective even in settings with high HIV prevalence (2-year OS: 55.5%).[17,34] Similarly, the strongest impact for all NHL was administration of at least 5 cycles of any chemotherapy. These results have to be interpreted with caution since poor clinical status and subsequent early death were more likely found in the group with few cycles or no therapy. Nevertheless, our findings underline the necessity of subtype-directed and guideline-recommended treatment initiation and thorough administration of chemotherapy. Widely spread out-of-pocket expenditure inhibits both the continuation of chemotherapy as well as the adequate management of therapy side effects.[7,34,35] Other reasons impeding completion of care include stigma of cancer disease[36,37] and fear of therapy,[38] travel distances to oncological centers,[39] frequent stock out of chemotherapy,[40] and supportive drugs.[22]

The association between guideline-concordant approaches and improved survival is an encouraging result of our cohort study, but the effect of treatment of any kind was small compared to patients without any therapy documented. An observation from Uganda did not find benefit of treatment on survival.[22] Though we were unable to find detailed data on side effects, we believe that infections and other toxicity-related side effects of chemo(immuno-)therapy overall reduce treatment benefits. Results of single-center NHL cohort studies show death from treatment-related complications in 9%-34% of patients.[18,20-22] Therefore, there may be a need for patient stratification including dose reduction management and supportive care to offer tailored approaches in low-resource settings and eventually improve survival. To inform data-driven policy change regarding patient-centered provision of care, eg, further investigating the benefit of rituximab on survival, multicentre studies across the region should be conducted to address these global oncology challenges in SSA.[41] In this context, it is important to note that our study confirms recent findings from SSA not showing the difference in survival between HIV-positive and -negative patients.[16-19] Further, neither stage, ECOG PS, initiation of any treatment nor completion of at least 5 cycles of chemotherapy were influenced by HIV status in our cohort (Chi square test).

(3) Quality of care varied considerably within and between sites in terms of guideline-concordance and outcome. Addis Ababa, Nairobi, and Namibia had highest 1-year OS amounting up to 76.3%, whereas for Eldoret and Bulawayo it was as low as 37.5%. Proportion of patients diagnosed with NHL subtype ranged from 94.1% in Namibia to 8.3% in Maputo.[24] Further, proportion of patients treated (any therapy) ranged from 71.6% (Nairobi) to 12.8% (Brazzaville), median number of cycles applied ranged from 6 to 1, and initiation of guideline-concordant treatment (including deviations) was found in some 30% of patients from Namibia, but in no patients from Maputo and Bamako. Radiotherapy was found in only 6.6% of all patients originating from 4 of 10 participating registries, matching availability of radiation at the time. This is in contrast to the actual need for radiotherapy that has been estimated up to 64% of NHL patients in low-and-middle income countries.[42]NHL survival trends in Western countries have tremendously improved in the last decades. For example, the 5-year-relative survival for US patients has continuously risen, from 56.3% in the period of 1990-1994[43] to 73.2% in 2011-2017.[6] Reasons include better understanding of lymphoma behavior, improved pathological and molecular diagnostics, a less harmful and more individualized therapy arsenal involving adapted polychemotherapy, monoclonal antibodies, targeted agents, bone marrow transplant, and, importantly, improved supportive care.

Our data explore varying levels of the provision of adequate care in 11 oncological centers on population level and may serve as a baseline for targeting site-specific gaps. Generally, concerted efforts for long-lasting improvement of NHL survival in SSA should address enhancing diagnostic capacity,[12,24] sustainable provision of guideline-recommended chemotherapy and elevation of oncological healthcare workforce,[44] supportive,[45] and palliative care.[46] Prospective studies should examine the applicability of NCCN Harmonized Guidelines and focus on local shortcomings currently impeding significant advances in NHL care in the region.[7]

Limitations and Strengths

The retrospective design of the study resulted in some limitations. First, imprecise staging, poor documentation, and early

loss to follow up were frequent and have been reported from centers elsewhere.[10,22,47] In 43.3% of patients it was not possible to acquire any additional information on diagnosis, treatment, or survival, limiting our report to registry baseline data. This might make some findings, eg, on clinical presentation, less precise than those from prospective, single-institution studies.[18-20,29] It remains a subject of speculation whether patients not traceable have been facing particularly inadequate care, or even no treatment at all—or, quite the opposite, they left the registration area, eg, to seek more appropriate treatment. However, we assume that these patients are few since all of our study areas were major cities, usually providing the best cancer care in the country. We did include both public and private hospitals, and we estimate the proportion of affluent patients able to afford treatment is abroad rather small. Another possible reason for the high loss of follow-up is the problematic archiving system. Many study centers do not have well-established systems to document, trace and archive cases, and lack electronic databases. Nevertheless, it seems more likely that for a large share of the untraced cases, no therapy and therefore no medical records were initiated. In patients traced with incomplete therapy, we presume that a majority discontinued treatment due to a variety of reasons discussed above. In this sense, we consider the high share of loss to follow-up and the constricted diagnostic and therapeutic data not only a limiting factor of this study but also an important finding disclosing the concerning situation of NHL care in SSA.

Second, our survival data may reflect some selection bias. Overestimation of treatment effects is likely: (1) Reverse Kaplan-Meier analysis displayed that treatment was not selected at random, as patients with poor health status may not have been eligible for standard therapy, and some of these patients were censored early. (2) Patients with early deaths did not receive therapy, and (3) degree of guideline-concordance was only assessed during survival time and not before survival time started (immortal time bias, also known as survival bias).[48] To reduce the overestimation of treatment effects and early deaths, we excluded patients surviving less than 1 month.[48] For completion of eg, 6 cycles of CHOP, patients would have had to survive and remain in care for 4 months compared to our median follow-up of 6 months. However, follow-up data of our cohort was too poor to define a longer cutoff, and other cutoffs studied showed little differences in survival analysis. (4) Additionally, the random assignment of treatment could not be realized due to the observational design of the study.

Third, due to the shortage in diagnostic workup, subclassification of almost 6 in 10 NHL was missing. Therefore, analysis of subtype-specific survival beyond OS was limited due to small patient numbers. We decided to hence limit in-depth calculations to the most frequent subtype, DLBCL.

There are important strengths to our study. First, we included a large population-based random sample of all NHL patients from 11 study centers involving both public and private institutions, not just those referred to specialist centers, and patients both with and without treatment. Second, the study involved a variety of countries in SSA, reflecting on a wide range of socioeconomic conditions and different health services in the region. Third, we were able to evaluate the impact of different treatment approaches—from guideline-concordant optimal therapy to none at all—on survival. This study is the first to create a link between NCCN Harmonized Guidelines and therapy actually received on the ground. It is, to our knowledge, the first population-based overview of cross-sectional and longitudinal data on therapy and outcome of NHL patients in real-world SSA.

Conclusion

Advanced disease and considerable share of unclassified NHL reflect the lack of lymphoma awareness among healthcare personnel, poor referral systems, low pathological capacity, and high expenses of diagnosis that are hardly affordable for patients in low- and middle-income countries. Only a small proportion of patients from our cohort received NCCN guideline-concordant therapy, and these had better outcomes. Our results confirmed previous findings from SSA settings with high HIV prevalence that HIV in NHL appears to not be associated with worsened survival. For policymakers as well as institutions in SSA, our results can be an important baseline to plan, implement and measure targeted investments for improved outcomes of NHL patients. Cost-effective step-wise implementation of programs to allow guideline-concordant care should include: capacity-building for NHL subtyping, provision of therapeutic agents, supportive care and oncological workforce, fulfilling nursing requirements, and careful patient-centered care. Population-based cancer registries will facilitate monitoring these services over time.

Acknowledgments

We acknowledge Dr. Donald Maxwell Parkin's sustained support in facilitating this study. We appreciate the cooperation of the cancer registries within the African Cancer Registry Network and their personnel to contribute their data to our study.

Funding

Intramural Funding from the Research Department of the American Cancer Society (Contract No. 43359), German Ministry for Economic and Development Cooperation (BMZ) through the ESTHER University and Hospital Partnership Initiative of German International Cooperation (GIZ, Project No. 13.2238.7-004.41). N.C.S.M. was given a doctorate stipend by German Academic Exchange Service (DAAD) and Roland Ernst Stiftung für Gesundheitswesen, L.H. was given a doctorate stipend by Bischöfliche Studienförderung Cusanuswerk, J.F. was given a doctorate stipend by Bayer Foundation. T.P.S was supported by Studienstiftung des Deutschen Volkes e.V. through his regular scholarship. The sponsors of this study are public or nonprofit organizations that support science in general. They had no role in gathering, analyzing, or interpreting the data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of Interest

The authors indicated no conflict of interest.

Author Contributions

Conception/design: N.C.S.M., E.J.K. Provision of study material or patients: A.Z., J.F.P., F.T., N.G.B., H.W., M.N., E.C., M.K., G.N., C.F.L., M.-T.A.-A. Collection and/or assembly of data: A.Z., J.F.P., F.T., N.G.B., H.W., M.N., E.C., M.K., G.N., C.F.L., M.-T.A.-A. Data analysis and interpretation: N.C.S.M., E.J.K., L.H., M.G., T.P.S., Y.W.J.-F., J.F., J.M., M.B., B.L., M.B., O.H., A.J. Manuscript writing: N.C.S.M., E.J.K., L.H., M.G., T.P.S., Y.W.J.-F., J.F., J.M., M.B., B.L., M.B., O.H., A.J. Final approval of manuscript: All authors.

Data Availability

Data supporting the findings in our study are available upon request. Requests will be evaluated by the AFCRN research committee. The data application process is outlined on the AFCRN website at http://afcrn.org/index.php/research/how-to-apply/76-research-collaborations.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

References

1. Mafra A, Laversanne M, Gospodarowicz M, et al. Global patterns of non-Hodgkin lymphoma in 2020. *Int J Cancer*. 2022;151(9):1474-1481.
2. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. https://doi.org/10.3322/caac.21492.
3. Parkin DM, Nambooze S, Wabwire-Mangen F, Wabinga HR. Changing cancer incidence in Kampala, Uganda, 1991-2006. *Int J Cancer*. 2010;126(5):1187-1195. https://doi.org/10.1002/ijc.24838.
4. Chokunonga E, Borok MZ, Chirenje ZM, Nyakabau AM, Parkin DM. Trends in the incidence of cancer in the black population of Harare, Zimbabwe 1991-2010. *Int J Cancer*. 2013Published March 4, 2013;133(3):721-729. https://doi.org/10.1002/ijc.28063.
5. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2014;136(5):E359-E386. https://doi.org/10.1002/ijc.29210.
6. Howlader N, Am Noone, Krapcho M, et al. *SEER Cancer Statistics Review, 1975-2016: Based on November 2018 SEER data submission*. https://seer.cancer.gov/csr/1975_2016/. Updated September 5, 2019. Accessed September 6, 2019.
7. Gopal S, Wood WA, Lee SJ, et al. Meeting the challenge of hematologic malignancies in sub-Saharan Africa. *Blood*. 2012;119(22):5078-5087. https://doi.org/10.1182/blood-2012-02-387092.
8. Perry AM, Perner Y, Diebold J, et al. Non-Hodgkin lymphoma in Southern Africa: review of 487 cases from The International Non-Hodgkin Lymphoma Classification Project. *Br J Haematol*. 2015;172(5):716-723. https://doi.org/10.1111/bjh.13885. https://pubmed.ncbi.nlm.nih.gov/26898194/.
9. Mwamba PM, Mwanda WO, Busakhala N, et al. AIDS-related non-Hodgkin's lymphoma in Sub-Saharan Africa: current status and realities of therapeutic approach. *Lymphoma*. 2012;2012. https://pubmed.ncbi.nlm.nih.gov/24205439/
10. Milligan MG, Bigger E, Abramson JS, et al. Impact of HIV infection on the clinical presentation and survival of non-Hodgkin lymphoma: a prospective observational study from Botswana. *J Global Oncol*. 2018;4:1-11. https://doi.org/10.1200/JGO.17.00084.
11. Zelenetz AD, Gordon LI, Abramson JS, et al. *NCCN harmonized guidelines for Sub-Saharan Africa: B-cell lymphoma*. https://www.nccn.org/harmonized/default.aspx. Updated August 30, 2019. Accessed September 5, 2019.
12. Naresh KN, Raphael M, Ayers L, et al. Lymphomas in sub-Saharan Africa—What can we learn and how can we help in improving diagnosis, managing patients and fostering translational research? *Br J Haematol*. 2011;154(6):696-703. https://doi.org/10.1111/j.1365-2141.2011.08772.x.
13. Wiggill TM, Mantina H, Willem P, Perner Y, Stevens WS. Changing pattern of lymphoma subgroups at a tertiary academic complex in a high-prevalence HIV setting: a South African perspective. *Journal of Acquired Immune Deficiency Syndromes (1999)*. 2011;56(5):460-466. https://doi.org/10.1097/QAI.0b013e31820bb06a.
14. Wiggill TM, Mayne ES, Willem P. Challenges in lymphoma diagnosis in HIV positive patients in the South African setting. *Transfusion and Apheresis Science: Official Journal of the World Apheresis Association: Official Journal of the European Society for Haemapheresis*. 2013;49(2):157-162.
15. Patel M, Philip V, Omar T, et al. The impact of Human Immunodeficiency Virus infection (HIV) on lymphoma in South Africa. *Journal of Cancer Therapy*. 2015;06(06):527-535. https://doi.org/10.4236/jct.2015.66057.
16. Montgomery ND, Liomba NG, Kampani C, et al. Accurate real-time diagnosis of lymphoproliferative disorders in Malawi through clinicopathologic teleconferences: a model for pathology services in Sub-Saharan Africa. *Am J Clin Pathol*., 2016;146(4):423-430. https://doi.org/10.1093/ajcp/aqw118.
17. Kimani S, Painschab MS, Kaimila B, et al. Safety and efficacy of rituximab in patients with diffuse large B-cell lymphoma in Malawi: a prospective, single-arm, non-randomised phase 1/2 clinical trial. *The Lancet Global Health*. 2021;9(7):e1008-e1016. https://doi.org/10.1016/S2214-109X(21)00181-9.
18. Painschab MS, Westmoreland KD, Kasonkanji E, et al. Prospective study of Burkitt lymphoma treatment in adolescents and adults in Malawi. *Blood Adv*. 2019;3(4):612-620. https://doi.org/10.1182/bloodadvances.2018029199.
19. Painschab MS, Kasonkanji E, Zuze T, et al. Mature outcomes and prognostic indices in diffuse large B-cell lymphoma in Malawi: a prospective cohort. *Br J Haematol*. 2018;184(3):364-372. https://doi.org/10.1111/bjh.15625.
20. Gopal S, Fedoriw Y, Kaimila B, et al. CHOP chemotherapy for aggressive non-Hodgkin lymphoma with and without HIV in the antiretroviral therapy era in Malawi. *PLoS One*. 2016;11(3):e0150445. https://doi.org/10.1371/journal.pone.0150445.
21. Zuze T, Ellis GK, Kasonkanji E, et al. Modified EPOCH for high-risk non-Hodgkin lymphoma in sub-Saharan Africa. *Cancer Medicine*, 2019;9(1):77-83. https://doi.org/10.1002/cam4.2631.
22. Bateganya MH, Stanaway J, Brentlinger PE, et al. Predictors of survival after a diagnosis of non-Hodgkin lymphoma in a resource-limited setting: a retrospective study on the impact of HIV infection and its treatment. *Journal of Acquired Immune Deficiency Syndromes (1999)*. 2011;56(4):312-319. https://doi.org/10.1097/QAI.0b013e31820c011a.
23. Parkin DM, Liu B. *African Cancer Registry Network*. https://afcrn.org/. Accessed September 6, 2019.
24. Mezger NCS, Feuchtner J, Griesel M, et al. Clinical presentation and diagnosis of adult patients with non-Hodgkin lymphoma in Sub-Saharan Africa. *Br J Haematol*. 2020;190(2):209-221. https://doi.org/10.1111/bjh.16575.
25. Wikimedia Commons. *BlankMap-Africa*. https://commons.wikimedia.org/wiki/File:BlankMap-Africa.svg. Updated October 27, 2019. Accessed December 16, 2019.
26. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non- Hodgkin lymphoma: the Lugano classification. *J*

Clin Oncol. 2014;32(27):3059-3067. https://doi.org/10.1200/jco.2013.54.8800.
27. Hallek M. Chronic lymphocytic leukemia. 2017 update on diagnosis, risk stratification, and treatment. *Am J Hematol*. 2017;92(9):946-965. https://doi.org/10.1002/ajh.24826.
28. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. *European Journal of Cancer (Oxford, England: 1990)*. 2004;40(15):2307-2316.
29. Mwanda WO, Orem J, Fu P, et al. Dose-modified oral chemotherapy in the treatment of AIDS-related non-Hodgkin's lymphoma in East Africa. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2009;27(21):3480-3488.
30. Witt P de, Maartens DJ, Uldrick TS, Sissolak G. Treatment outcomes in AIDS-related diffuse large B-cell lymphoma in the setting roll out of combination antiretroviral therapy in South Africa. *Journal of Acquired Immune Deficiency Syndromes (1999)*. 2013;64(1):66-73.
31. Okello CD, Omoding A, Ddungu H, Mulumba Y, Orem J. Outcomes of treatment with CHOP and EPOCH in patients with HIV associated NHL in a low resource setting. *BMC cancer*. 2020;20(1):798. https://doi.org/10.1186/s12885-020-07305-2.
32. Stopeck AT, Unger JM, Rimsza LM, et al. A phase 2 trial of standard-dose cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) and rituximab plus bevacizumab for patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: SWOG 0515. *Blood*. 2012;120(6):1210-1217. https://doi.org/10.1182/blood-2012-04-423079.
33. Schulz H, Bohlius J, Skoetz N, et al. Chemotherapy plus rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma. *The Cochrane Database of Systematic Reviews*. 2007;(4):CD003805. https://pubmed.ncbi.nlm.nih.gov/17943799/
34. Painschab MS, Kohler R, Kimani S, et al. Comparison of best supportive care, CHOP, or R-CHOP for treatment of diffuse large B-cell lymphoma in Malawi: a cost-effectiveness analysis. *The Lancet Global Health*. 2021;9(9):e1305-e1313. https://doi.org/10.1016/S2214-109X(21)00261-8.
35. Painschab MS, Kohler RE, Kasonkanji E, et al. Microcosting analysis of diffuse large B-cell lymphoma treatment in Malawi. *J Global Oncol*. 2019;5:1-10. https://doi.org/10.1200/JGO.19.00059.
36. Anakwenze C, Bhatia R, Rate W, et al. Factors related to advanced stage of cancer presentation in Botswana. *J Global Oncol*. 2018;4:1-9. https://doi.org/10.1200/JGO.18.00129.
37. Gakunga R, Kinyanjui A, Ali Z, et al. Identifying barriers and facilitators to breast cancer early detection and subsequent treatment engagement in Kenya: a qualitative approach. *The Oncologist*. 2019;24(12):1549-1556. https://doi.org/10.1634/theoncologist.2019-0257.
38. Martei YM, Vanderpuye V, Jones BA. Fear of mastectomy associated with delayed breast cancer presentation among Ghanaian Women. *The Oncologist*. 2018;23(12):1446-1452. https://doi.org/10.1634/theoncologist.2017-0409.
39. Ellis GK, Manda A, Topazian H, et al. Feasibility of upfront mobile money transfers for transportation reimbursement to promote retention among patients receiving lymphoma treatment in Malawi. *International Health*. 2021;13(3):297-304. https://doi.org/10.1093/inthealth/ihaa075.
40. Gopal S. Moonshot to Malawi. *N Engl J Med*. 2016;374(17):1604-1605. https://doi.org/10.1056/NEJMp1601982.
41. Mbulaiteye SM. Safety and efficacy of rituximab in Malawi: a case for multicentre oncology clinical trials in Africa? *Lancet Global Health*. 2021;9(7):e895-e896. https://doi.org/10.1016/S2214-109X(21)00210-2.
42. Barton MB, Frommer M, Shafiq J. Role of radiotherapy in cancer control in low-income and middle-income countries. *Lancet Oncol*. 2006;7(7):584-595. https://doi.org/10.1016/S1470-2045(06)70759-8.
43. Sant M, Allemani C, Angelis R de, et al. Influence of morphology on survival for non-Hodgkin lymphoma in Europe and the United States. *European Journal of Cancer (Oxford, England: 1990)*. 2008;44(4):579-587.
44. Wilson BE, Jacob S, Yap ML, et al. Estimates of global chemotherapy demands and corresponding physician workforce requirements for 2018 and 2040: a population-based study. *Lancet Oncol*. 2019;20(6):769-780. https://doi.org/10.1016/S1470-2045(19)30163-9.
45. Lyman GH, Crawford J, Tomita D, Whittaker S, Dale DC. Changing patterns of chemotherapy relative dose intensity and supportive care for aggressive B-cell non-Hodgkin lymphoma. *Leukemia & Lymphoma*. 2015;57(2):283-290. https://doi.org/10.3109/10428194.2015.1045894.
46. van der Plas WY, Benjamens S, Kruijff S. The increased need for palliative cancer care in Sub-Saharan Africa. *European Journal of Surgical Oncology*. 2020;46(7):1373-1376.
47. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *The Lancet*. 2018;391(10125):1023-1075.
48. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol*. 2007;167(4):492-499. https://doi.org/10.1093/aje/kwm324.

Breast Cancer Diagnostics, Therapy, and Outcomes in Sub-Saharan Africa: A Population-Based Registry Study

Joko-Fru WY, Griesel M, Mezger NCS, Hämmerl L, Seraphin TP, Feuchtner J, Wabinga H, N'da G, Mathewos A, Kamaté B, Nsonde Malanda J, Gnangnon FHR, Chesumbai GC, Korir A, Lorenzoni C, Zietsman A, Borok MZ, Liu B, Thomssen C, McGale P, Jemal A, Parkin DM, Kantelhardt EJ. Breast Cancer Diagnostics, Therapy, and Outcomes in Sub-Saharan Africa: A Population-Based Registry Study. J Natl Compr Canc Netw. 2021 Dec 29;20(13). doi: 10.6004/jnccn.2021.7011. PMID: 34965508

Volltext: https://jnccn.org/view/journals/jnccn/19/13/article-p75.xml

Abstract

Background: Breast cancer (BC) is the most common cancer in sub-Saharan Africa (SSA). However, little is known about the actual therapy received by women with BC and their survival outcome at the population level in SSA. This study aims to describe the cancerdirected therapy received by patients with BC at the population level in SSA, compare these results with the NCCN Harmonized Guidelines for SSA (NCCN Harmonized Guidelines), and evaluate the impact on survival.

Methods: Random samples of patients with BC (≥40 patients per registry), diagnosed from 2009 through 2015, were drawn from 11 urban population-based cancer registries from 10 countries (Benin, Congo, Cote d'Ivoire, Ethiopia, Kenya, Mali, Mozambique, Namibia, Uganda, and Zimbabwe). Active methods were used to update the therapy and outcome data of diagnosed patients ("traced patients"). Excess hazards of death by therapy use were modeled in a relative survival context.

Results: A total of 809 patients were included. Additional information was traced for 517 patients (63.8%), and this proportion varied by registry. One in 5 traced patients met the minimum diagnostic criteria (cancer stage and hormone receptor status known) for use of the NCCN Harmonized Guidelines. The hormone receptor status was unknown for 72.5% of patients. Of the traced patients with stage I-III BC (n=320), 50.9% received inadequate or no cancer-directed therapy. Access to therapy differed by registry area. Initiation of adequate therapy and early-stage diagnosis were the most important determinants of survival.

Conclusions: Downstaging BC and improving access to diagnostics and care are necessary steps to increase guideline adherence and improve survival for women in SSA. It will also be important to strengthen health systems and facilities for data management in SSA to facilitate patient follow-up and disease surveillance.