Non-Hodgkin-Lymphome in Subsahara-Afrika: Eine multinationale populationsbasierte Kohortenstudie zu Diagnostik, Therapiequalität und Überleben

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Referat

Non-Hodgkin-Lymphome (NHL) sind die sechsthäufigste Malignomart in Subsahara-Afrika (SSA). Aufgrund der heterogenen Biologie der über 80 verschiedenen NHL werden sehr unterschiedliche Therapieansätze empfohlen. In SSA ist die Prognose im globalen Vergleich schlecht. Deshalb haben wir die Diagnose- und Therapiequalität im Zusammenhang mit dem Gesamtüberleben (*overall survival*: OS) auf Bevölkerungsebene in der Region untersucht. In dieser retrospektiven Beobachtungsstudie wurden in elf populationsbasierten Krebsregistern in zehn Ländern (Äthiopien, Benin, Côte d'Ivoire, Kenia, Republik Kongo, Mali, Mosambik, Namibia, Simbabwe und Uganda) 516 NHL-Patient:innen aus den Jahren 2011-2015 eingeschlossen. Die vorliegenden Krebsregisterdaten wurden durch klinische Informationen auf Basis von Krankenakten ergänzt. Die onkologische Therapie (cancer-directed therapy: CDT) wurde im Hinblick auf die Einhaltung der für SSA ressourcenstratifizierten Leitlinien des National Comprehensive Cancer Network untersucht und die Assoziation mit dem OS mit multipler Cox-Regression modelliert. Die Lymphom-Diagnose wurde in 76,2 % histologisch, in 17,3 % zytologisch und in 6,5 % rein klinisch gestellt. Von 516 NHL konnten 57,9 % nicht subtypisiert werden, bei 42,1 % wurde ein Subtyp festgelegt. In der subtypisierten Gruppe waren hoch-maligne B-Zell-Lymphome, insbesondere das diffuse großzellige B-Zell-Lymphom (DLBCL), am häufigsten, gefolgt von niedrig-malignen B-Zell-Lymphomen, T-Zell- und anderweitig klassifizierten Lymphomen. Von allen Patient:innen erhielten 37,8 % eine CDT. Diese war in 4,1 % von 516 strikt leitlinienkonform, während sie in 9,5 % geringfügig abwich. Bei 75,1 % war keine Therapiebewertung möglich: Bei 43,2 % konnten keine Krankenakten gefunden werden, 27,8 % waren nicht subtypisiert, für 4,1 % lagen keine Leitlinien vor. Leitlinienkonforme Behandlung war am häufigsten in Namibia (30,8 %), am seltensten in Mali und Mosambik (je 0 %). Für alle NHL mit Nachbeobachtung > 1 Monat (n = 296) waren weniger als 5 Zyklen systemischer Therapie sowie überhaupt keine Therapie mit einem schlechteren OS verbunden. Ähnlich waren für DLBCL (n = 74) sowohl nicht leitlinienkonforme als auch keine Therapie mit schlechterem Überleben assoziiert. Diese populationsbasierte Studie stellt als erste ihrer Art in SSA fest, dass die meisten Patient:innen keinen Zugang zu adäquater Behandlung haben. Ein Dreiklang aus verbesserten Kapazitäten für Diagnosestellung, Zugang zu systemischer sowie symptomatischer Therapie könnte wesentlich für die Verbesserung der Prognose von Patient:innen mit Non-Hodgkin- Lymphomen in SSA sein.

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Abstract

Non-Hodgkin lymphoma (NHL) is the sixth most common malignancy in sub-Saharan Africa (SSA). Due to the heterogeneous biology among over 80 NHL subtypes, a variety of treatment approaches is available. Prognosis in SSA is poor by global standards. Therefore, we assessed diagnostic and treatment quality and its association with overall survival (OS) on population level in the region. In this retrospective observational longitudinal study we included 516 patients randomly sampled from eleven population-based cancer registries in ten countries (Benin, Congo, Côte d'Ivoire, Ethiopia, Kenya, Mali, Mozambique, Namibia, Uganda, and Zimbabwe) and diagnosed between 2011 and 2015. Cancer-directed therapy (CDT) was assessed for concordance with resource-stratified National Comprehensive Cancer Network guidelines and its association with OS was modelled with multiple Cox regression. Based on histology in 76.2%, cytology in 17.3%, and mere clinical evaluation in 6.5%, 57.9% of 516 NHL could not be further classified, while a subtype was identified in 42.1%. Within the latter group, aggressive B-cell lymphoma, namely mostly diffuse large B-cell lymphoma (DLBCL), were most common, followed by low-malignant B-cell lymphoma, T-cell and otherwise sub-classified NHL. Of all patients, 37.8% received CDT. Concordance with guidelines was identified in 4.1% of the 516 patients, deviations thereof in 9.5%. Assessment for guideline concordance was not possible in 75.1%: medical records could not be traced in 43.2%, 27.8% lacked sub-classification, and resource-stratified guidelines were not available in 4.1%. Guideline-stratified treatment was most common in Namibia (30.8%) and least common in Mali and Mozambique (0%, respectively). For all NHL patients with follow-up > 1 month (n=296), less than 5 cycles of systemic therapy and no therapy were associated with lower OS. Similarly, for DLBCL (n=74), both non-guideline concordant and no therapy were associated with worse survival. This study is the first of its kind in SSA to highlight that most patients do not have access to adequate diagnosis and treatment. A triad of improved capacity for comprehensive diagnosis, access to adequate systemic therapy, and supportive care may be essential for improving the prognosis of patients with NHL in SSA.

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1. Einleitung und Zielstellung

1.1 Malignome und ihre bevölkerungsbasierte Überwachung

Krebserkrankungen waren 2019 für 250 Millionen verlorene gesunde Lebensjahre (*disability-adjusted life years*) weltweit verantwortlich.[1] Die Entstehung von Krebs ist mit individuellen Faktoren wie Alter, Lebensstil und weiteren Erkrankungen verbunden, unterliegt aber auch Umwelteinflüssen. Überlebens- und Heilungschancen hängen nicht nur von der Krebsart, sondern insbesondere vom Zugang zu adäquater Diagnostik und Therapie ab. Um die hohe Belastung durch Krebserkrankungen zu reduzieren, steht staatlichen Gesundheitssystemen ein Portfolio an Interventionen zur Verfügung, die von Präventions- und Früherkennungsprogrammen bis hin zum Aufbau von Palliativversorgung das *continuum of cancer care* stärken können.[2] Für die Überwachung solcher nationalen Pläne sammeln bevölkerungsbasierte Krebsregister an ausgewählten Zentren Daten zu Häufigkeit und Schwere von Krebserkrankungen sowie zu Versorgungsqualität und Überlebensdauer. Dadurch lässt sich die Wirksamkeit der Maßnahmen im zeitlichen Verlauf beurteilen. Der Stellenwert von bevölkerungsbasierten Krebsregistern wird auch im subsaharischen Afrika (SSA) zunehmend anerkannt. Allerdings bestehen sowohl im internationalen als auch regionalen Vergleich bislang erhebliche Unterschiede in Organisation und Finanzierung der Register sowie Verfügbarkeit und Qualität der Daten: in 2018 wurden für 17 Länder in der Region aufgrund fehlender Daten Schätzungen auf Basis von Nachbarländern vorgenommen[3], und 2015 erreichten 19 von 26 Registern weniger als fünf von 15 Qualitätskriterien.[4] Das African Cancer Registry Network (AFCRN) ist Teil des Internationalen Netzwerks für Krebsbehandlung und -forschung (INCTR), das mit Unterstützung der Internationalen Krebsforschungsagentur (IARC) nationale und regionale Register bei Aufbau, Ausbildung und Datenauswertung unterstützt, um Forschungsplattformen für die Ermittlung von Problemen, Prioritäten und Interventionszielen zu schaffen.[5] Gemeinsam mit den Krebsregistern ist das AFCRN Kooperationspartner dieser Arbeit.

1.2 Krebs in Subsahara-Afrika

Zu Subsahara-Afrika zählen rund 50 Staaten, die überwiegend zu den Ländern mit niedrigem und mittlerem Einkommen[6] gehören und etwa 1,1 Milliarden Menschen mit einer Lebenserwartung von zurzeit rund 62 Jahren beherbergen.[7] Die rasante Veränderung von Lebensgewohnheiten, Wohlstand und Lebenserwartung in der Region geht einher mit einer Verschiebung des Spektrums von übertragbaren hin zu nicht-übertragbaren Krankheiten. Seit 1990 ist die Inzidenzrate metabolischer, kardiovaskulärer und onkologischer Erkrankungen stetig gestiegen[8], und bis 2040 wird von einer Verdopplung der absoluten Anzahl der Krebsneuerkrankungen in SSA im Vergleich zu 2018 ausgegangen.[9] Die in Ländern mit hohem

Einkommen etablierten Standards bei Diagnostik und Therapie von Malignomen können oft nicht umgesetzt werden, was zu bis vierfach höheren Mortalitätsraten bei einzelnen Krebsentitäten führt und die ohnehin stark belasteten Gesundheitssysteme der Region vor massive Herausforderungen stellt.[10] Für das Jahr 2030 wird von fast 800 000 Krebstoten in SSA ausgegangen.[11]

1.3 Das Non-Hodgkin-Lymphom in Afrika

Pathophysiologie: Non-Hodgkin-Lymphome (NHL) sind eine heterogene Krankheitsgruppe, die maligne monoklonale Proliferationen lymphatischer Zellen in lymphoretikulärem Gewebe umfasst. Seltener sind extranodale Lymphome z.B. im Gastrointestinaltrakt und, insbesondere im Zusammenhang mit AIDS, im zentralen Nervensystem. Die meisten (80-90 %) NHL entstehen aus B-Lymphozyten, der Rest aus T-Lymphozyten oder natürlichen Killerzellen. Generell wird zwischen hoch-malignen (aggressiven) und niedrig-malignen (indolenten) NHL unterschieden.[12]

Subtypen: In der jüngsten Überarbeitung des NHL-Klassifikationssystems unterscheidet die WHO über 80 Subtypen.[12] Im weltweiten Vergleich treten Subtypen unterschiedlich häufig auf[13], im Allgemeinen zählen jedoch das diffuse großzellige B-Zell Lymphom (DLBCL), das follikuläre Lymphom (FL) sowie die chronische lymphatische Leukämie (CLL) zu den häufigsten Subtypen. Ein internationales Projekt zur Klassifikation von NHL untersuchte 487 konsekutive Fälle im südlichen Afrika: im Vergleich zu Westeuropa und Nordamerika waren hoch-maligne B-Zell Lymphome häufiger.[14] Für die verschiedenen Subtypen liegen unterschiedlichste Therapieansätze vor, die von *watchful waiting* über alleinige Bestrahlung bis hin zu Hochdosischemotherapie reichen.

Inzidenz: Im Jahr 2019 waren in den Vereinigten Staaten von Amerika hämatologische Malignome für 9,0 % bzw. 9,5 % der landesweiten Krebs-Inzidenz und -Mortalität verantwortlich.[15] Im Vergleich trugen hämatologische Malignome im Jahr 2020 in SSA anteilig zu 9,0 % der Krebs-Inzidenz und 9,1 % der Mortalität bei.[16] Innerhalb der hämatologischen Malignome ist die Gruppe der NHL jeweils am häufigsten, und über alle Krebsarten hinweg in SSA die sechsthäufigste Krebsart.[16] Einen differenzierteren Blick erlaubt die Angabe der alterstandardisierten Häufigkeit von Krebsneuerkrankungsraten. Für Regionen innerhalb von SSA reichten im Jahr 2020 die altersstandardisierten NHL-Inzidenzraten von 3,6 im zentralen Afrika bis 5,8/100.000 Einwohner:innen und Jahr im südlichen Afrika. Im Vergleich lag die altersstandardisierte Inzidenzrate in den USA mit 12,1 bis zu dreimal so hoch. Insgesamt nehmen die Inzidenzraten von NHL in SSA weiterhin leicht zu.[17] Die genaue Ätiologie von NHL ist überwiegend unbekannt, allerdings spielen umweltbedingte, demografische, ethnische und Lebenswandel-Faktoren eine wichtige Rolle.[18] Bedeutsam ist, dass in SSA 19,7 % der NHL-Fälle mit Infektionserregern assoziiert sind.[19] Allein 12,7 % der Fälle werden dem humanen

Immundefizienzvirus (HIV) zugeordnet, wenngleich die genaue Pathogenese bisher bei keinem Subtyp geklärt ist.[20] Diese epidemiologische Assoziation mit NHL bleibt auch bestehen, wenn die HI-Viruslast durch antiretrovirale Medikamente kontrolliert wird.[21] Weiterhin sind NHL ätiologisch mit dem humanen Gammaherpesvirus 8, Helicobacter pylori, dem humanen T-lymphotropen Virus 1 und Malaria sowie epidemiologisch mit dem Epstein-Barr-Virus und dem Hepatitis-C-Virus assoziiert.[22] Zusätzlich spielt die synergische Onkogenität von Mischinfektionen eine Rolle für bösartige hämatologische Erkrankungen, wie sie etwa für HIV und EBV bekannt ist.[23] Nicht zuletzt hängt die steigende Inzidenz in SSA vermutlich auch mit zunehmenden Möglichkeiten der Diagnostik und einer insgesamt verbesserten Datenlage zusammen.[11,24]

Überleben: Da Rezidivfreiheit auf Bevölkerungsebene oft nicht messbar ist, wird in der Epidemiologie meist die Überlebensdauer, also der Zeitraum von Diagnose bis zum Todeszeitpunkt untersucht. Bei fehlender Information zur Todesursache wird meist die allgemeine Überlebensdauer (*overall survival)* genutzt. Diese wiederum kann an die Grundsterblichkeit der Bevölkerung in verschiedenen Altersgruppen adjustiert werden.[25] Die allgemeine Überlebensdauer kann darüber hinaus für die jeweilige Krebsart altersadjustiert werden.[26] Dies führt zu (altersstandardisierten) relativen Überlebensraten ((AS)RS), welche die Möglichkeit des Vergleichs zwischen Populationen international und im zeitlichen Verlauf erlauben. In Ländern mit hohem Einkommen werden heute bei hämatologischen Malignomen noch nie dagewesene Raten des langfristigen Überlebens erreicht. In den USA wird für die Gesamtheit der NHL eine Verbesserung der relativen 5-Jahres-Überlebensrate unabhängig vom Stadium von 56 % im Zeitraum 1990-1994[27] auf 73 % im Zeitraum 2011-2017 beschrieben.[28] Zu den Gründen gehören ein besseres Verständnis der Biologie, eine genauere histologische und molekulare Diagnostik, ein nebenwirkungsärmeres und stärker individualisiertes Therapiearsenal mit angepasster Polychemotherapie, monoklonalen Antikörpern, zielgerichteten Wirkstoffen, Stammzelltransplantation und einer verbesserten supportiven Therapie, um die mit der Therapie einhergehenden Nebenwirkungen abzumildern. Allerdings sind die Strukturen und Ressourcen zur Nutzung dieser Innovationen in SSA unzureichend. Damit einher geht ein deutlich geringeres Überleben. In vielen Ländern SSAs sind keine Personenstandregister vorhanden, weshalb bevölkerungsbasierte Krebsregister Überleben mittels Telefonanrufen erfassen. Für SSA liegen bisher weder subtypspezifische Überlebensraten im Speziellen noch relative 5-Jahres-Überlebensraten für NHL im Allgemeinen auf Bevölkerungsebene vor.[24] Kleine, monozentrische und krankenhausbasierte Studien berichten von 1-Jahres-Überleben für alle NHL-Patient:innen von 54 % in Botswana[29] und 68 % für DLBCL in Malawi.[30] Auf Bevölkerungsebene lässt sich lediglich die altersstandardisierte, jedoch nicht für Lymphome als Todesursache adjustierte Mortalität vergleichen: Diese reichte 2020 in den afrikanischen Regionen von 2,6 bis 3,5 pro 100.000

Einwohner:innen und Jahr, in den USA betrug sie – bei zwei- bis dreimal höherer Inzidenzrate – 2,8 pro 100.000.[24]

1.4 Verfügbare Ressourcen

Trotz der zunehmenden Erfordernisse sind die Ressourcen für die Diagnose, Behandlung und Palliation von NHL in SSA knapp. Der Anteil der Ausgaben für Gesundheitsleistungen gemessen am Bruttoinlandsprodukt betrug 2019 durchschnittlich 5,0 % in der Region, in Deutschland 9,1 %. Absolut bezifferten sich die Gesundheitsausgaben auf nur auf 80 US-Dollar pro Einwohner:in und Jahr, in Deutschland 5440.[31] Die onkologische Versorgung konzentriert sich auf Großstädte, obwohl 2021 58 % der Bevölkerung SSAs in ländlichen Gebieten lebten,[32] sowie auf wirtschaftlich fortgeschrittenere Länder.

Hämatopathologie: Die sehr unterschiedlichen Therapieansätze für die verschiedenen Lymphom-Typen erfordern eine differenzierte pathologische Diagnose. Leider können die meisten pathologischen Labore in SSA dies nicht leisten[17], da vor Ort meist nur einfache Lichtmikroskopie zur Verfügung steht.[33] Daher wird davon ausgegangen, dass Lymphome in Ländern mit niedrigem und mittlerem Einkommen unterdiagnostiziert sind.[24,34] Damit einher geht auch eine häufige Verwechslung mit durch Infektionskrankheiten hervorgerufener benigner Lymphadenopathie.[35] Der Mangel an Patholog:innen ist symptomatisch für den kritischen Mangel an medizinischem Personal in der Region. Im afrikanischen Durchschnitt gibt es drei Patholog:innen pro Million Einwohner:innen.[36] In einer Studie zu Lymphom-Diagnostik-Infrastruktur der nationalen Referenzkrankenhäuser von vier Ländern SSAs von 2011 wurden unter anderem fehlende Ausbildungsmöglichkeiten, lange Bearbeitungszeiten, eine heterogene Laborausstattung sowie mangelnde Möglichkeiten für Immunhistochemie gefunden. Dennoch konnten 93 % von 393 Lymphom-Diagnosen anhand histologischer Präparate unabhängig bestätigt werden.[34] Allerdings bleibt die Subtypisierung von Lymphomen, welche oftmals auf Immunhistochemie sowie weiterführenden zytogenetischen, molekularen und FISH-Techniken basiert, eine Herausforderung in der Region.[23] Somit bleibt die Therapie der zahlreichen NHL-Entitäten, für die ein breites Spektrum an Therapiealgorithmen entwickelt wurde, hinter ihren Möglichkeiten zurück: Anhand hoch-maligner B-Zell-Lymphome lässt sich die Bedeutung einer genauen Diagnose verdeutlichen. DLBCL kann mit einer CHOP-Chemotherapie (Cyclophosphamid, Vincristin, Doxorubicin und Prednisolon) gut behandelt werden, auch im afrikanischen Kontext.[37] Optimal wäre wie in Ländern mit hohem Einkommen sehr wahrscheinlich die Hinzunahme des monoklonalen Antikörpers Rituximab. Andere Subtypen wie das Burkitt-Lymphom (BL) oder das plasmablastische Lymphom, welche häufiger bei HIV-positiven Patient:innen vorkommen, haben schlechtere Ergebnisse mit einer CHOP-Chemotherapie, sprechen aber besser auf intensivere Chemotherapie-Schemata an, die in SSA wahrscheinlich ebenfalls sicher

verabreicht werden können.[38–40] Empfehlungen für die Behandlung von nicht klassifizierten Lymphomen gibt es nicht.

Chemotherapie: Da es sich bei NHL um systemische Erkrankungen handelt, hat Chemotherapie einen zentralen Stellenwert in der Behandlung. Insbesondere die in SSA häufigen hoch-malignen Lymphome sprechen in der Regel gut auf Chemotherapie an, auch noch in fortgeschrittenen Stadien.[41] Fehlende Verfügbarkeit von Chemotherapeutika in SSA hängt mit Lieferengpässen und Kosten zusammen. Daneben kursieren in Ländern mit niedrigem und mittlerem Einkommen häufig gefälschte und minderwertige Arzneimittel.[23] Um eine sichere und effektive Chemotherapie in SSA durchführen zu können, bedarf es insbesondere auch geschulten Personals, Ausrüstung sowie einer ausreichend ausgebauten Infrastruktur. In SSA gab es 2015 lediglich 102 Institutionen, die eine onkologische Versorgung anbieten, wobei sich allein 38 in der Republik Südafrika befanden.[42] Chancen bestehen in der Dezentralisierung: Mit angemessener Unterstützung können auch Ärzt:innen ohne onkologische Facharztausbildung und Pflegekräfte, die in ländlichen Gebieten ohne Onkolog:innen arbeiten, Chemotherapie vor Ort sicher und wirksam verabreichen, nachdem eine (tele-)pathologische Diagnose und fachärztliche Therapieentscheidung gestellt wurde.[43]

Antikörper: Die Behandlungsprotokolle für die meisten B-Zell-Lymphome enthalten monoklonale CD-20-Antikörper, die für mehrere Subtypen in die Liste unentbehrlicher Arzneimittel der WHO aufgenommen wurden[44] und nachweislich die Überlebenszeit verbessern.[45] Allerdings ist Rituximab in Ländern mit niedrigem und mittlerem Einkommen meist mit dem Risiko hoher Verschuldung für die Patient:innen behaftet.[46] Ein möglicher Weg zur Senkung der Kosten ist die Verwendung von Biosimilars.[30]

Strahlentherapie: Für einige niedrig-maligne und manche lokal begrenzte hoch-maligne Lymphome ist eine Heilung durch Strahlentherapie oder kombinierte Radiochemotherapie möglich. Auch als palliativer Therapieansatz hat Bestrahlung einen Stellenwert.[47] Im Jahr 2020 hatten 28 von 54 Ländern SSAs Zugang zur externen Strahlentherapie, allerdings teils mit älteren Geräten.[48] Damit sind 18 % des Strahlentherapie-Bedarfs in SSA gedeckt, wobei bis zu 64 % der NHL-Patient:innen in Ländern mit niedrigem und mittlerem Einkommen eine Bestrahlung benötigen.[49]

Stammzelltransplantation: Bei Rezidiven hoch-maligner NHL ist eine Hochdosis-Chemotherapie mit anschließender hämatopoetischer Stammzelltransplantation (HSZT) indiziert. 2011 erfolgten HSZT in sechs Zentren in SSA (alle in Südafrika), mit vergleichbaren Ergebnissen zu Ländern mit hohem Einkommen.[50] Der Aufbau einer Infrastruktur für HSZT ist in weiten Teilen SSAs in naher Zukunft wahrscheinlich nicht machbar. Denkbar wären Strategien zur Ausweitung der autologen HSZT auf ausgewählte Patient:innen in nationalen Referenzkrankenhäusern oder in regionalen Zentren, die multinationale Blöcke versorgen.[23]

Onkologische Chirurgie: Die onkologische Chirurgie hat nur bei selteneren Subtypen therapeutische Relevanz, spielt aber eine wichtige Rolle in der Diagnostik. Weltweit steht einem Großteil der Krebspatient:innen bezahlbare und zeitgerechte Chirurgie nicht zur Verfügung [51], in SSA ist dieser Anteil mit über 90% der Patient:innen am größten. [52]

Watchful waiting: Bei langsam wachsenden asymptomatischen niedrig-malignen NHL wird oftmals eine abwartende Beobachtungsstrategie (*watchful waiting*) verfolgt, bei der die Patienten regelmäßig untersucht, aber zunächst nicht behandelt werden. In SSA werden allerdings die meisten NHL in einem symptomatischen Stadium diagnostiziert, bei dem eine Therapie indiziert ist.[23]

Logistische Hürden: In allen Staaten SSAs lebt ein Großteil der Bevölkerung in ländlichen Gegenden.[32] Zentren mit onkologischen Behandlungsmöglichkeiten befinden sich allerdings nahezu ausschließlich in großen Städten, sind nicht selten in privater Hand und somit geographisch wie finanziell lediglich für einen kleineren Teil der Bevölkerung zugänglich.[23] In ländlichen Gebieten ist die onkologische Versorgung substanziell eingeschränkt, etwa aufgrund mangelnder onkologischer Kenntnisse des Gesundheitspersonals, fehlenden diagnostischen Möglichkeiten und eingeschränkter Patientenüberweisung, weshalb Krebserkrankungen in späten Stadien erkannt werden.[53]

Kulturelle Unterschiede: Kulturelle Normen und lokale Traditionen können zusätzlich den Zugang zum Gesundheitssystem und damit eine zeitnahe Diagnosestellung und kurative onkologische Therapie erschweren. In einer südafrikanischen Studie konsultierten bis zu 80 % der Teilnehmenden vor Vorstellung in staatlichen Gesundheitseinrichtungen eine:n traditionellen Heilpraktiker:in.[54]

Soziale Unterschiede: Das mediane Alter von Patient:innen mit NHL betrug in SSA in verschiedenen Studien zwischen 37 und 47 Jahren.[29,37–41] So sind Menschen in wirtschaftlich produktivem Alter betroffen. Die kostenaufwendige Behandlung geht zulasten der lokalen Gesundheitssysteme, muss in den meisten Fällen aufgrund fehlender Krankenversicherung bzw. *universal health coverage* in SSA allerdings von den Familien der Erkrankten getragen werden und führt bisher regelhaft zur Verarmung.[55]

1.5 Zielstellung

In der Einleitung sind Hindernisse für eine adäquate onkologische Versorgung von Patient:innen mit NHL in SSA angeführt worden. Zahlreiche Studien weisen auf steigende Inzidenzen von Krebserkrankungen und unzureichende onkologische Infrastruktur in SSA hin. Jedoch ist dem Autor zum Zeitpunkt der Schriftlegung dieser Arbeit keine populationsbezogene Studie über die hämatoonkologische Versorgung von individuellen

Patient:innen mit NHL in SSA bekannt. Der erste Teil der dargelegten Studie untersuchte daher die Qualität der klinischen und pathologischen Diagnostik von NHL und die Verteilung der Subtypen. Im zweiten Abschnitt wurde der Frage nachgegangen, wie leitlinienadhärent Patient:innen mit NHL behandelt wurden und wie der Zusammenhang zwischen Leitlinienadhärenz und Überleben war. Ziel war es, zu untersuchen, ob die aufgezählten Probleme eine leitliniengerechte Versorgung in der Breite der Bevölkerung verhindern und letztlich das Überleben beeinträchtigen. Somit sollte ein umfassendes Bild der Lymphom-Versorgung in SSA gezeichnet werden, um letztlich auf Möglichkeiten der Verbesserung der medizinischen Versorgung aufmerksam zu machen.

2. Diskussion

2.1 Pathologische Diagnostik

Die Ergebnisse zur pathologischen Diagnostik zeigen, dass in SSA noch nicht überall der Mindeststandard erreicht wird: Bei eine:r von sechs Patient:innen der untersuchten Kohorte bildeten eine Feinnadelaspirationszytologie und bei eine:r von 15 Patient:innen ausschließlich klinische Informationen die Grundlage für die NHL-Diagnose. Obwohl eine Zytologie in SSA aufgrund geringerer Kosten und leichterer Durchführbarkeit unabhängig von Chirurg:innen weitverbreitet zu sein scheint[34], gilt sie als erheblich ungenauer als eine Biopsie und schränkt weiterführende Untersuchungen ein.[56] Immunhistochemie wird in SSA beispielsweise beim Mammakarzinom zunehmend routinemäßig eingesetzt und ist auch für die Subtypisierung von NHL essentiell. Diese ist Voraussetzung für den Einsatz subtypspezifischer Therapiealgorithmen. Deshalb ist der hohe Anteil von 57,9 % nicht klassifizierter Lymphome, für die es keine Behandlungsempfehlung gibt, sehr nachteilig. In krankenhausbasierten Studien aus Botswana und Uganda wurde über wesentlich niedrigere Raten von nicht klassifizierten Lymphomen berichtet (13-14 %)[29,40], während eine andere Studie aus Nigeria Subtypisierung gar nicht erst erwähnte[57], was eine fehlende Klassifizierung wahrscheinlich macht. In mehreren Studien aus Malawi war Subtypisierung ein Einschlusskriterium.[30,38,39,41,58,59] Unser populationsbasierter Ansatz zeigt hingegen, dass in der Breite offenbar ein schwerwiegender Mangel an angemessener Lymphom-Charakterisierung besteht. Dies ist Folge des Defizits an pathologischer Infrastruktur, ausgebildetem Personal und hohen Kosten. In der Folge haben die NCCN Guidelines for Sub-Saharan Africa den Mangel an Immunhistochemie-Kapazitäten aufgenommen und angepasste Empfehlungen gegeben. Sie befürworten ein immunhistochemisches Mindest-Panel, das CD-20, Ki-67 und CD-45 beinhaltet, mit dem sich vor allem B- von T-Zell-Lymphomen sowie hoch- von niedrig-malignen und somit heilbare von nicht heilbaren NHL unterscheiden lassen.[60] Pilotprojekte in SSA nutzen ein ähnlich ressourcenangepasstes Modell: Ein aus lediglich neun Antikörpern bestehendes immunhistochemisches Panel kombiniert mit telepathologischen Konsultationen konnte eine Übereinstimmung lokal erfolgter Subtypisierung mit in den USA gestellten Diagnosen von über 90 % zeigen.[58]

2.2 Subtypverteilung

Der hohe Anteil hoch-maligner B-Zell-Lymphome (55,8 %) in unserer Studie steht im Einklang mit anderen Studien aus SSA.[14,29,34,58,61–63] Dieser Anteil blieb in unserer Studie auch nach Altersadjustierung weiterhin höher (48,3 %) als in den US-amerikanischen SEER-Daten (31,3 %).[64] Die Hypothese, dass HIV, dessen Prävalenz in manchen Ländern unserer Studie 15 % und mehr beträgt, ein wichtiger Faktor für die Genese von HIV-assoziierten hoch-malignen B-Zell-Lymphomen in SSA ist, konnten wir mit einer Korrelationsanalyse untermauern. Diese

aggressiven Lymphome führen unbehandelt schnell zum Tod, die Häufigkeit hoch-maligner B-Zell-Lymphome bietet durch das Heilungspotenzial aber auch Chancen. Mit der vergleichsweise kostengünstigen systemischen und mit verbesserter supportiver Therapie wird für DLBCL in den USA für den Zeitraum 2008-2013 ein relatives 5-Jahres-Überleben von 64 % berichtet.[65] Eine effiziente Behandlung gerade dieser jüngere Menschen betreffenden hoch-malignen Lymphome könnte auch die Auswirkungen auf die Volkswirtschaften verringern.

2.3 Klinische Diagnostik

In SSA stellen sich Patient:innen meist mit fortgeschrittener Lymphom-Erkrankung vor. So wurden in unserer Kohorte fast drei Viertel im fortgeschrittenen Stadium (III oder IV nach Ann-Arbor und Stadium C nach Binet) diagnostiziert, fast zwei Drittel waren in schlechtem Allgemeinzustand (ECOG performance score ≥2), und vier von fünf in unserer Kohorte berichteten von B-Symptomen. Ursachen für die späte Diagnosestellung umfassen ein geringes Bewusstsein für Lymphome unter Gesundheitspersonal und damit zusammenhängende schlechte Überweisungsmechanismen zu Tertiärkrankenhäusern.[66] Selbst in Botswana, einem Land mit mittlerem Einkommen, vergingen zwischen den ersten Lymphom-Symptomen und der endgültigen Diagnose eines NHL durchschnittlich 280 Tage.[29] Eine Studie aus Uganda berichtete sogar davon, dass 30,6 % von 183 Lymphom-Patient:innen für im Median 3,5 Monate gegen Tuberkulose behandelt wurden, ehe eine Lymphom-Diagnose gestellt wurde.[67]

Wurde in unserer Kohorte ein Lymphom diagnostiziert, wurden häufig keine bildgebenden Verfahren, kein Staging und kein HIV-Test durchgeführt (59,4 %, 39,2 % und 47,4 %). In SSA haben Patient:innen nicht zuverlässig Zugang zu Röntgen und Ultraschall, geschweige denn zu weiterführenden bildgebenden Verfahren. Daher besteht bei Untersuchungen zu Kohorten in SSA der Verdacht, dass das schlechte Überleben auch mit *Understaging* zusammenhängen könnte. Eine Verbesserung der klinischen Untersuchung könnte die personalisierte Therapieentscheidung verbessern.

2.4 Therapie

Ein alarmierendes Ergebnis unserer Untersuchung war, dass bei fast zwei Dritteln der Patient:innen trotz gründlicher Datensammlung keine dokumentierte gegen das Lymphom gerichtete Therapie (systemische Therapie; Strahlentherapie; lymphomgerichtete Chirurgie – cancer-directed therapy: CDT) festgestellt werden konnte. Es ist wahrscheinlich, dass bei einem wesentlichen Teil dieser Patient:innen auch tatsächlich keine Therapie erfolgt ist. Von den Patient:innen unserer Kohorte mit CDT erhielten fast alle CHOP- (73,0 %) oder COP-basierte (12,6 %) Therapien.[68] Diese kostengünstigen Chemotherapeutika stehen seit langem auf der Liste der unentbehrlichen Krebsmedikamente, weitere teurere wie z.B. das

hochwirksame Bendamustin für CLL wurden jüngst aufgenommen.[69,70] Dennoch sind sowohl Kosten als auch Verfügbarkeit von Chemotherapeutika wichtige Faktoren, die zur undifferenzierten Therapie in SSA beitragen. Manche Zytostatika sind gar nicht verfügbar, für CHOP-Zytostatika werden Lieferengpässe in den Apotheken berichtet.[40,66] In Botswana waren 2015 mindestens 40 % der essentiellen Chemotherapeutika für eine mediane Zeit von einem Monat nicht verfügbar. In Äthiopien betrug die mediane Wartezeit von Diagnose bis zum Beginn der Chemotherapie zwei Monate.[71] Für die Betroffenen bedeutet dies eine Verzögerung von Therapiezyklen, eine Reduktion der Zyklenanzahl oder Substitution mit weniger effektiven Chemotherapeutika und letztlich schlechteres Outcome.[72] In diesem Zusammenhang ist hervorzuheben, dass Patient:innen in unserer Kohorte im Median 6 Zyklen systemischer Therapie (Interquartilsabstand 3 – 6) erhielten und eine Therapie mit 5 oder mehr Zyklen auch mit verbessertem Überleben assoziiert war. Dies spricht dafür, dass bei Patient:innen, bei denen aufgrund mutmaßlich günstiger finanzieller Voraussetzungen, einem besseren Allgemeinzustand, dem Engagement von Behandelnden oder anderer Umstände eine Therapie eingeleitet wurde, die Behandlung relativ gut toleriert und von ihr profitiert wurde, sodass mehrere Zyklen verabreicht werden konnten. Wenngleich es in unserer Studie nicht möglich war, Daten zu Nebenwirkungen der Therapie und supportiven Maßnahmen zu erheben, müssen Maßnahmen zur Verbesserung der onkologischen Versorgung diese Aspekte in den Blick nehmen. In SSA besteht Ungewissheit über optimale Zytostatikadosierungen bei gleichzeitig ungenügender supportiver Therapie[23] – welche auch kostenrelevant ist. In Malawi kostete jede Episode neutropenischen Fiebers im Rahmen der Behandlung eines DLBCL schätzungsweise 236 US-Dollar. Angesichts der Vielzahl an Studien aus SSA, die über frühzeitige Todesfälle durch Komplikationen im Rahmen der Lymphom-Therapie berichten[30,38–40,59], vermuten wir, dass der geringe Effekt jeglicher systemischer Therapie auf das Überleben in unserer Studie teilweise mit diesen Nebenwirkungen zusammenhängt.

2.5 Leitlinienadhärenz

Von den Patientinnen mit einem dokumentierten Überleben von mindestens einem Monat erhielt nur etwa ein Fünftel eine den Leitlinien entsprechende oder davon leicht abweichende CDT, also eine subtypspezifische systemische Therapie, die immerhin von einem Sechstel beendet werden konnte. Zwischen den einzelnen Ländern variierte der Anteil der Patient:innen, die eine leitliniengerechte Therapie erhielten, zwischen 30,8 % in Namibia und je 0 % in Mali und Mosambik. Neben den oben diskutierten begrenzten hämatopathologischen Möglichkeiten ist also von relevant unzureichenden Kapazitäten in der hämatologisch-onkologischen systemischen Therapie auszugehen. Wesentliche Verbesserungen hin zu leitliniengerechter Therapie könnte die Bereitstellung von Antikörpern gegen den auf den meisten B-Zell Lymphomen exprimierten CD-20 Rezeptor bieten, die in Ländern mit hohem

Einkommen zu noch nie dagewesenen Raten der langfristigen Heilung und Kontrolle von B-Zell-Lymphomen geführt haben.[73] Diese auch im subsaharischen Kontext wahrscheinlich sicher einsetzbaren und kosteneffektiven[74] CD-20 Antikörper sind in den harmonisierten NCCN-Leitlinien für mehrere B-Zell-Lymphom-Subtypen enthalten, und die Kosten für Biosimilars sind in der Regel niedriger. In unserer Studie wurden CD-20 Antikörper nur bei 3,9 % der Patient:innen verabreicht, bei einer B-Zell Lymphom-Prävalenz von 35,9 % in der gesamten Kohorte. Im Rahmen der Bestrebungen hin zur Aufnahme von Prävention, Früherkennung, Therapie und Nachsorge von onkologischen Erkrankungen in nationalen *Universal Health Coverage* Plänen[75] sollte erwogen werden, neben einem Mindeststandard an Diagnostik für NHL auch Therapeutika wie CD-20 Antikörper in Ländern mit niedrigem und mittlerem Einkommen bereitzustellen. Somit könnte der Zugang zu leitliniengerechter Therapie für die in SSA hochprävalenten B-Zell Lymphome auch für benachteiligte Bevölkerungsgruppen in SSA sichergestellt und die in SSA häufig für ganze Familien zu Verarmung führenden sogenannten *catastrophic health expenditures*[76] vermieden werden. In Namibia deckt die öffentliche Krankenversicherung das Medikament seit 2013 ab, wo die meisten aller mit CD-20 Antikörpern behandelten Patient:innen in unserer Kohorte lebten.

2.6 Überleben und Einflussfaktoren

Eine Analyse der Überlebensraten ergab ein 1- und 3-Jahres- ASRS von 62,3 % und 32,9 %. Bisher liegen der Kenntnis des Autors zufolge Vergleichsdaten für Länder mit niedrigem und mittlerem Einkommen nur aus Äthiopien, Zimbabwe und Indien vor (3-Jahres-ASRS 36,5 %, 20,8 % und 40,8 %).[77] Eine Angabe für das 5-Jahres-ASRS war aufgrund der unzureichenden Nachverfolgung weder in unserer Studie noch in den WHO-Angaben möglich. Im Vergleich dazu sind Schätzungen von 73,8 % 5-Jahres-ASRS für die USA im Zeitraum 2012-2018 und von 65,6 % 5-Jahres-ASRS für Großbritannien in 2013-2017 als Beispiele für Länder mit hohem Einkommen wesentlich höher. Über alle Patient:innen mit NHL hinweg hatten Personen mit fortgeschrittener Erkrankung (schlechter Allgemeinzustand (ECOG PS>1), B-Symptomatik und fortgeschrittenem Stadium) eine schlechtere Überlebenswahrscheinlichkeit (adjustierte HRR jeweils >1,9). Dementgegen war eine Infektion mit HIV sogar mit einem leichten Überlebensvorteil assoziiert (adjustierter HRR 0,81), was darauf hinweisen könnte, dass die HIV-erkrankten Patient:innen unserer Kohorte, die nahezu alle zum Zeitpunkt der Lymphom-Diagnose bereits antiretroviral behandelt wurden, einen etwas besseren Zugang zu Gesundheitsversorgung haben könnten. Allerdings standen weder das Stadium, der ECOG PS, der Beginn einer Behandlung noch der Abschluss von mindestens 5 Chemotherapiezyklen im Zusammenhang mit dem HIV-Status (Chi-Quadrat-Test). Andere im letzten Jahrzehnt publizierte Studien aus SSA konnten ebenfalls keinen Überlebensnachteil von NHL-Patient:innen mit HIV zeigen, wenn diese antiretroviral therapiert wurden.[30,39,40,59] Während kein klarer Überlebensvorteil für Patient:innen mit jeglicher Therapie gegenüber solchen ohne

Therapie gezeigt werden konnte, waren weniger als 5 Zyklen systemischer Therapie sowie keine Therapie im Vergleich zu 5 oder mehr Zyklen mit einem deutlich schlechteren Überleben assoziiert (adjustierte HRR 2,6 und 2,3). Dieses Ergebnis sollte aufgrund des *survivorship-bias* mit Vorsicht interpretiert werden[78] – in der Gruppe mit 5 oder mehr Zyklen waren nur solche, die nicht vorher verstorben waren. Hinsichtlich der Subtypen unterschied sich das mediane Überleben deutlich. Entgegen der Erwartung, dass Patient:innen mit hoch-malignen NHL schnell versterben, war das Überleben von Patient:innen mit DLBCL (medianes Überleben 48 Monate) besser als bei jenen mit CLL (40) und FL (9), während jenes von Patient:innen mit BL (8) erwartbar niedrig war. Möglicherweise beruht das schlechte Überleben von SSA-Patient:innen mit niedrig-malignen Lymphomen im Vergleich zu europäischen oder US-amerikanischen Daten auch darauf, dass diese Lymphom-Typen in Ländern mit hohem Einkommen häufig bei Routineuntersuchungen und in frühen- asymptomatischen Stadien diagnostiziert werden (*lead-time-bias*[79]), in SSA dagegen in fortgeschrittenen symptomatischen Stadien. Als Proxy-Parameter für eine bessere Versorgung untersuchten wir den Einfluss der Subtypisierung im Allgemeinen, konnten allerdings im Vergleich nur einen leichten Überlebensnachteil von unklassifizierten NHL finden (adjustierter HRR 1,28). Der Zusammenhang der Leitlinienkonformität mit dem Überleben wurde zur Biasminimierung nur bei der Gruppe von 74 Patient:innen mit DLBCL und ≥1 Monat Beobachtungszeit und adjustiert für bekannte prognostische Faktoren analysiert. Hier zeigte sich ein klarer Vorteil der leitliniengerecht mit CHOP und Rituximab oder abweichend mit CHOP behandelten Patient:innen im Vergleich zu anderweitig (HRR 11,34) und nicht (HRR 11,75) behandelten Patient:innen. Im Jahr 2019 erstellte das NCCN „harmonisierte“ Leitlinien für ressourcenarme Regionen wie SSA. 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 kaum in einer randomisierten Studie untersucht werden. Vor diesem Hintergrund unterstützt der in der vorliegenden Studie beobachtete Zusammenhang zwischen höherem Grad der Therapieadhärenz und besserem Überleben die Grundsätze dieser Leitlinien, die bei Bedarf spezifische Abweichungen von der Maximalversorgung nahelegen, und welche das Bewertungsschema der vorliegenden Studie ebenfalls vorsah. Da zeitnah kein flächendeckender Zugang zu Maximalversorgung in der Lymphom-Therapie in SSA zu erwarten ist, erscheint also die Anwendung der „harmonisierten“ Leitlinien empfehlenswert.

2.7 Stärken und Limitationen

Limitationen dieser Arbeit sind die teils fehlende Dokumentation von Diagnostik sowie Therapie in den SSA-Zentren und ein kurzes Follow-up von im Median lediglich 70 Tagen, was allerdings in vergleichbaren Studien in SSA ebenfalls berichtet wird. Wir gehen davon aus, dass die erreichte Datenvollständigkeit den Umständen entsprechend mit adäquatem Aufwand

nicht zu verbessern ist. Aufgrund des retrospektiven Studienansatzes war es nicht möglich, eine direkte Kausalität aus den Analysen abzuleiten. Die Daten wurden zu Einwohner:innen aus Großstädten erhoben und sind somit nur mit großer Einschränkung auf die ländlichen Regionen übertragbar, weil der Zugang zur Versorgung von Krebserkrankungen dort noch eingeschränkter ist. Bei der Regressionsanalyse liegt wahrscheinlich ein *survivor-bias* vor: Nach 30 Tagen waren 40 Patient:innen verstorben, nach 60 Tagen weitere 13, nach 90 Tagen zusätzliche 11. Diese Patient:innen hatten mutmaßlich eine geringere Chance, eine Therapie zu beginnen und trugen somit möglicherweise zur Verschlechterung des Überlebens in der Gruppe ohne jegliche CDT bei. In einer diesbezüglichen Sensitivitätsanalyse, bei der wir Patient:innen ausschlossen, deren Nachverfolgung statt unter einem Monat unter zwei, drei und sechs Monaten war, sahen wir in der adjustierten Regressionsanalyse allerdings ähnlich große Effektstärken der Vervollständigung einer systemischen Therapie auf das Überleben. Daneben ist zudem von einen *survivor-bias* zugunsten derjenigen Patientinnen auszugehen, die eine vollständige Behandlung erhalten hatten. Deshalb wurde entschieden, in die Regressionsanalyse nur Patientinnen mit einer mindestens einmonatigen Überlebenszeit nach Diagnose einzubeziehen. Damit wurde versucht, der Überschätzung des Therapieeffekts etwas zu begegnen,[79] was allerdings auch zum Ausschluss von 218 Patient:innen (42,2% der populationsbasierten Kohorte) führte. Eine weitere Einschränkung ist, dass Patient:innen eine Behandlung möglicherweise nicht zufällig begannen, sondern beeinflusst von mit dem Überleben zusammenhängenden *Confoundern* wie z.B. Co-Morbiditäten und sozioökonomischen Faktoren, für die allerdings aufgrund der eingeschränkten Datenlage nicht adjustiert werden konnte. Auf der anderen Seite ist eine wesentliche Stärke dieser Arbeit, dass Patient:innen durch Stichproben aus bevölkerungsbasierten Registern ausgewählt wurden. Es wird daher vermutet, dass die vorliegende Studie im Vergleich zu krankenhausbasierten Studien einem geringeren Selektionsbias unterliegt. Die Ergebnisse ähneln denen vergleichbarer Studien, etwa hinsichtlich der Stadienverteilung, des Überlebens und des Anteils HIV-positiver Patient:innen[29,30,38–40,46,59], was auf Repräsentativität hinweist. Der Umstand des schnellen Versterbens nach Diagnose gibt Hinweise darauf, dass Patient:innen sich zum einen erst mit fortgeschrittener Erkrankung vorstellen und zum anderen eine formale Diagnose verspätet erfolgt. Insofern kann im Vergleich zu Daten aus Ländern mit hohem Einkommen bei den vorliegenden Studienergebnissen von geringem *lead-time-bias* ausgegangen werden.

2.8 Fazit und Ausblick

Wir haben gezeigt, dass NHL-Patient:innen in SSA zum Großteil nicht ausreichend versorgt werden und sich fehlende und unvollständige Diagnostik und Therapie negativ auf das Überleben auswirken. Das fortgeschrittene Krankheitsstadium und der hohe Anteil nicht klassifizierter NHL spiegeln das mangelnde Bewusstsein der Bevölkerung und des

Gesundheitspersonals für Lymphome, schlechte Überweisungssysteme, geringe pathologische Kapazitäten und hohe Kosten wider, die für Patient:innen in SSA kaum erschwinglich sind. Kosteneffiziente Programme, die schrittweise eine leitlinienkonforme Versorgung ermöglichen, sollten eine Krankenversicherung für alle Menschen, den Aufbau von Mindestkapazitäten für die Lymphom-Subtypisierung, die Bereitstellung von hämatoonkologischen sowie supportiven Therapeutika sowie die Ausbildung onkologischen Personals umfassen. Zukünftige prospektive populationsbasierte Untersuchungen mit weiter reduziertem Bias sollten Einblicke in die Entwicklung der Therapiequalität und deren Einfluss auf das Überleben geben und systematisch Gründe für ein Abweichen von Leitlinienempfehlungen erfassen.

Abschließend hoffen wir, dass unsere Studien Politiker:innen, Gesundheitspersonal und Patientenorganisationen weitere Argumente für die Verbesserung der Versorgung von Krebspatient:innen in SSA an die Hand geben.

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4. Thesen

1. Ein Subtyp konnte für zwei Fünftel (42,1 %, n = 217) aller Non-Hodgkin-Lymphome (NHL) identifiziert werden, während die übrigen (57,9 %, n = 299) unklassifiziert blieben. Innerhalb der subtypisierten NHL waren hoch-maligne B-Zell Lymphome am häufigsten (55,8 %, n = 121), gefolgt von niedrig-malignen B-Zell-Lymphomen (29,5 %, n = 64).
2. Fast zwei Drittel (63,0 %, n = 97) der getesteten NHL-Patient:innen waren HIV-positiv. Es wurde eine moderate Korrelation zwischen der landesspezifischen HIV-Prävalenz und der Prävalenz HIV-assoziierter hoch-maligner B-Zell-Lymphome gefunden (Pearson-Korrelation r=0,61).
3. Bei fast drei Vierteln (73,0 %, n = 130) der untersuchten NHL-Patient:innen wurde ein fortgeschrittenes Stadium (Ann-Arbor III/IV und Binet C) festgestellt.
4. Jegliche Form onkologischer Therapie (cancer-directed therapy, CDT) konnte in knapp zwei Fünfteln (37,8 %, n = 195) festgestellt werden, bei den übrigen (62,2 %, n = 321) war keine Therapie dokumentiert. Bei NHL-Patient:innen, die jegliche Form von systemischer Therapie (Chemotherapie und/oder Immuntherapie) erhielten (36,2 %, n = 187), wurden im Median 6 Zyklen (Interquartilsabstand 3-6) verabreicht.
5. Bei 4,1 % (n = 21) wurde der Beginn einer mit den ressourcenstratifizierten NCCN-Leitlinien strikt konformen Therapie identifiziert, bei weiteren 9,5 % (n = 49) der Beginn einer von den Leitlinien geringfügig abweichenden Therapie.
6. Bei 75,1 % (n = 388) war keine Therapiebewertung möglich: bei 43,2 % (n = 223) konnten keine Krankenakten gefunden werden, weitere 27,8 % (n = 143) waren nicht subtypisiert, für die übrigen 4,1 % (n = 21) lagen keine Leitlinien vor.
7. Das allgemeine 1- und 3-Jahres-Überleben betrug 61,2 % (95 % Konfidenzintervall (KI) 52,9 % – 70,4 %) und 37,2 % (95 % KI 30,5 % – 43,9 %).
8. Für alle NHL-Patient:innen mit Nachbeobachtung von über einem Monat (n = 296) waren weniger als 5 Zyklen systemischer Therapie sowie überhaupt keine Therapie mit einem niedrigeren allgemeinem Überleben assoziiert.
9. Für alle NHL-Patient:innen mit Diagnose eines diffusen großzelligen B-Zell Lymphoms und Nachbeobachtung von über einem Monat (n = 74) waren sowohl nichtlinienadhärente als auch überhaupt keine Therapie mit geringerem allgemeinen Überleben assoziiert.
10. Eine bekannte HIV-Infektion war nach Adjustierung für andere Faktoren wie Stadium und Therapie nicht mit einem Überlebensnachteil assoziiert.

Publikationsteil

Beschreibung der eigenen Leistung

Diese Arbeit ist Teil der „Therapy and Outcome Study“ als gemeinsames Projekt der Martin-Luther-Universität Halle-Wittenberg, des Afrikanischem Krebsregisternetzwerks und der einzelnen Register. Dabei habe ich als letzter von fünf Doktorand:innen die Datensammlung in Namibia und in der Republik Kongo koordiniert. Daten zu fünf Krebsarten wurden in allen Registern gesammelt und für jede Entität ausgewertet. Für die vorgelegte Dissertation wurde der Fokus auf meine Erstautorschaften (Publikation 1 und 2) mit Fokus auf NHL gelegt.

Publikation 1 und 2:

1. **Mezger NCS**, Feuchtner J, Griesel M, Hämmerl L, Seraphin TP, Zietsman A, Péko JF, Tadesse F, Buziba NG, Wabinga H, Nyanchama M, Borok MZ, Kéita M, N'da G, Lorenzoni CF, Akele-Akpo MT, Gottschick C, Binder M, Mezger J, Jemal A, Parkin DM, Wickenhauser C, Kantelhardt EJ. Clinical Presentation and Diagnosis of Adult Patients with Non-Hodgkin Lymphoma in Sub-Saharan Africa. Br J Haematol. 2020 Jul;190(2):209-221. doi: 10.1111/bjh.16575.
2. **Mezger NCS**; Hämmerl L, Griesel M, Seraphin TP, Joko-Fru YW, Feuchtner J, Zietsman A, Péko JF, Tadesse F, Buziba NG, Wabinga H, Nyanchama M, Chokunonga E, Kéita M, N'da G, Lorenzoni CF, Akele-Akpo MT, Mezger JM, Binder M, Liu B, Bauer M, Henke O, Jemal A, Kantelhardt EJ. Guideline Concordance of Treatment and Outcomes Among Adult Non-Hodgkin Lymphoma Patients in Sub-Saharan Africa: A Multinational, Population-Based Cohort. Oncologist. 2023 Jun 27:oyad157. doi: 10.1093/oncolo/oyad157.

Mein Beitrag als Autor:

Studienkonzeption; Datenerhebung, Koordination in zwei von elf beteiligten Krebsregistern (Windhoek (Namibia) und Brazzaville (Kongo)) von Dezember 2017 bis Mai 2018; Datenanalyse; federführendes Erstellen des Manuskripts.

Publikation 3, 4, 5 und 6:

3. Griesel M, Seraphin TP, **Mezger NCS**, Hämmerl L, Feuchtner J, Joko-Fru WY, Sengayi-Muchengeti M, Liu B, Vuma S, Korir A, Chesumbai GC, Nambooze S, Lorenzoni CF, Akele-Akpo MT, Ayemou A, Traoré CB, Wondemagegnehu T, Wienke A, Thomssen C, Parkin DM, Jemal A, Kantelhardt EJ. Cervical Cancer in Sub-Saharan

Africa: A Multinational Population-Based Cohort Study of Care and Guideline Adherence. Oncologist. 2021 May;26(5):e807-e816. doi: 10.1002/onco.13718.

4. Seraphin TP, Joko-Fru WY, Hämmerl L, Griesel M, **Mezger NCS**, Feuchtner JC, Adoubi I, Egué MD, Okerosi N, Wabinga H, Hansen R, Vuma S, Lorenzoni C, Coulibaly B, Odzebe SW, Buziba NG, Aynalem A, Liu B, Medenwald D, Mikolajczyk RT, Efstathiou JA, Parkin DM, Jemal A, Kantelhardt EJ. Presentation, patterns of care, and outcomes of patients with prostate cancer in sub-Saharan Africa: A population-based registry study. Cancer. 2021 Nov 15;127(22):4221-4232. doi: 10.1002/cncr.33818.

5. 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.

6. Hämmerl L, **Mezger NCS**, Seraphin TP, Joko-Fru WY Griesel M, Feuchtner J, Gnahatin F, Gnangnon FHR, Okerosi N, Amulen MP, Hansen R, Borok MZ, Carrilho C, Mallé B, Ah Clausina AA, Buziba NG, Seife E, Liu B, Mikolajczyk R, Parkin DM, Kantelhardt EJ, Jemal A. Treatment and survival among colorectal cancer patients in sub-Saharan Africa: A multicentric population-based follow-up study. J Natl Compr Canc Netw vol. 21,9 (2023): 924-933.e7. doi:10.6004/jnccn.2023.7041.

Mein Beitrag als Autor:

Studienkonzeption, Datenerhebung in zwei von elf beteiligten Krebsregistern (Windhoek (Namibia) und Brazzaville (Kongo)), Mitarbeit bei Datenanalyse und Erstellen des Manuskripts.

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 31.08.2024	Nikolaus Christian Simon Mezger 

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Stockholm, im August 2024
Nikolaus Mezger

Originalpublikationen

1. Mezger et al., Clinical presentation and diagnosis of adult patients with non-Hodgkin lymphoma in Sub-Saharan Africa. Br J Haematol. 2020.

2. Mezger et al., Guideline Concordance of Treatment and Outcomes Among Adult Non-Hodgkin Lymphoma Patients in Sub-Saharan Africa: A Multinational, Population-Based Cohort. Oncologist. 2023.

3. Griesel et al., Cervical Cancer in Sub-Saharan Africa: A Multinational Population-Based Cohort Study of Care and Guideline Adherence. Oncologist. 2021.

4. Seraphin et al., Presentation, patterns of care, and outcomes of patients with prostate cancer in sub-Saharan Africa: A population-based registry study. Cancer. 2021.

5. Joko-Fru et al., Breast Cancer Diagnostics, Therapy, and Outcomes in Sub-Saharan Africa: A Population-Based Registry Study. J Natl Compr Canc Netw. 2021.

6. Hämmerl et al, Treatment and survival among colorectal cancer patients in sub-Saharan Africa: A multicentric population-based follow-up study. J Natl Compr Canc Netw. 2023.

bjh research paper

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

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Summary

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

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

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Introduction

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

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

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

Patients and methods

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

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

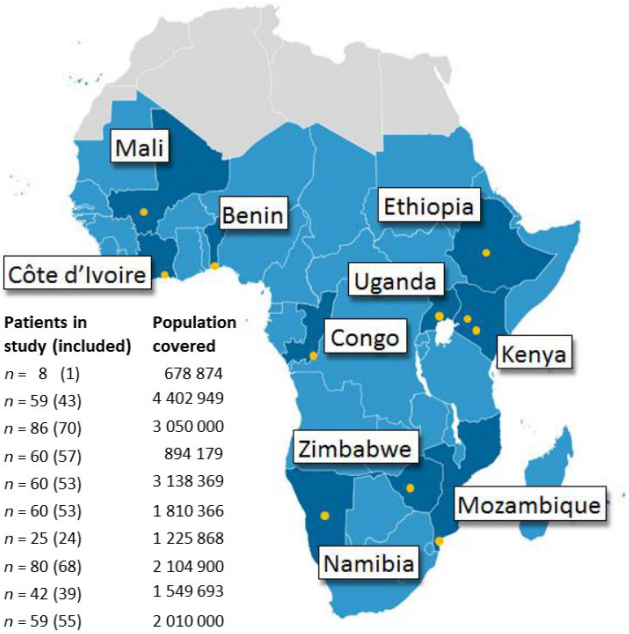
registries due to lack of patients. In total, 1068 patients were available in the registry databases. We assessed prevalence of adequate care from medical records among a random sample that could be assessed within feasible time and efforts in the given setting. We intended to draw conclusions for an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

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

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

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

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



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

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

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

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

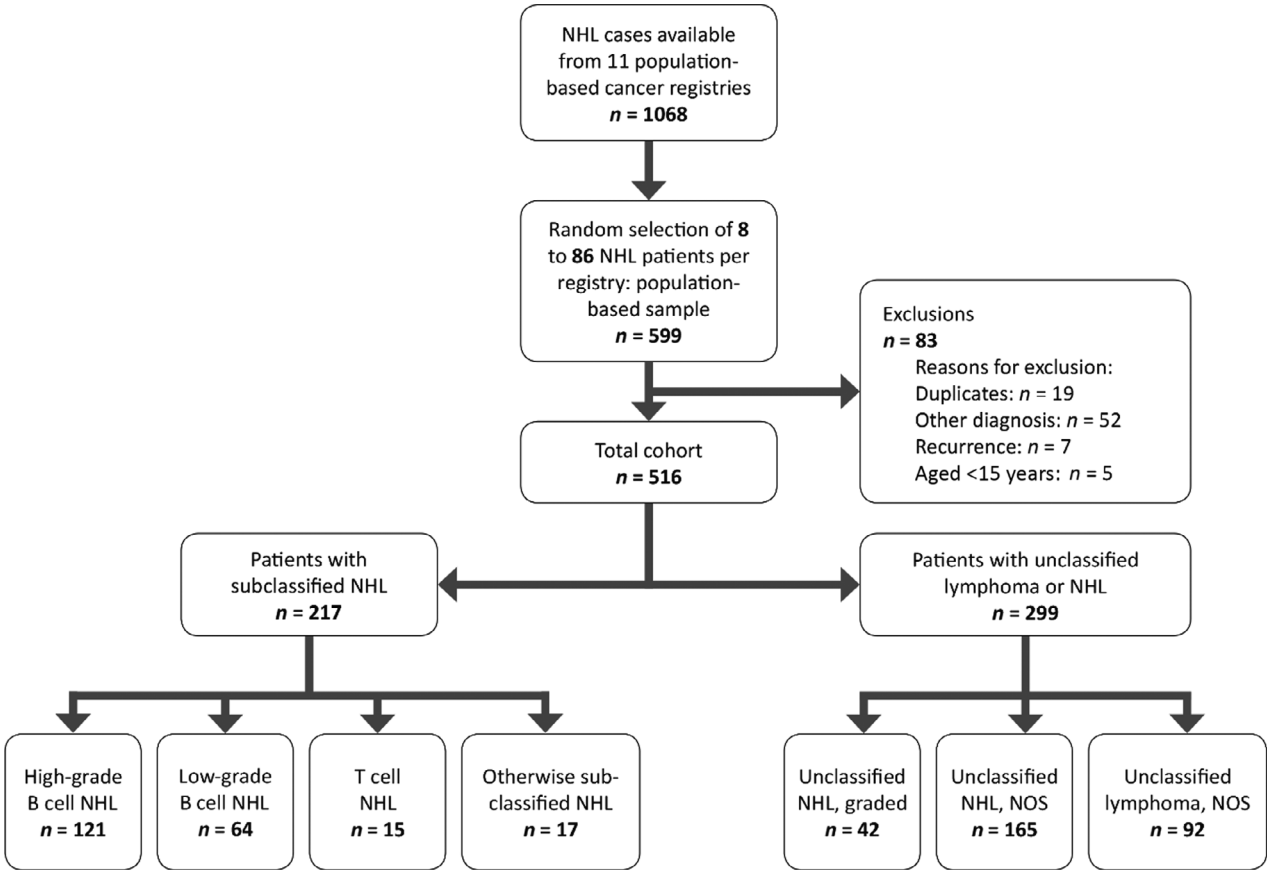


Fig. 2. Flowchart of study population. Stratified by non-Hodgkin lymphoma groups. NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

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

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

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

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

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

*Percentage of all subclassified NHL.

†Percentage of total cohort.

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

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

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

Results

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

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

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

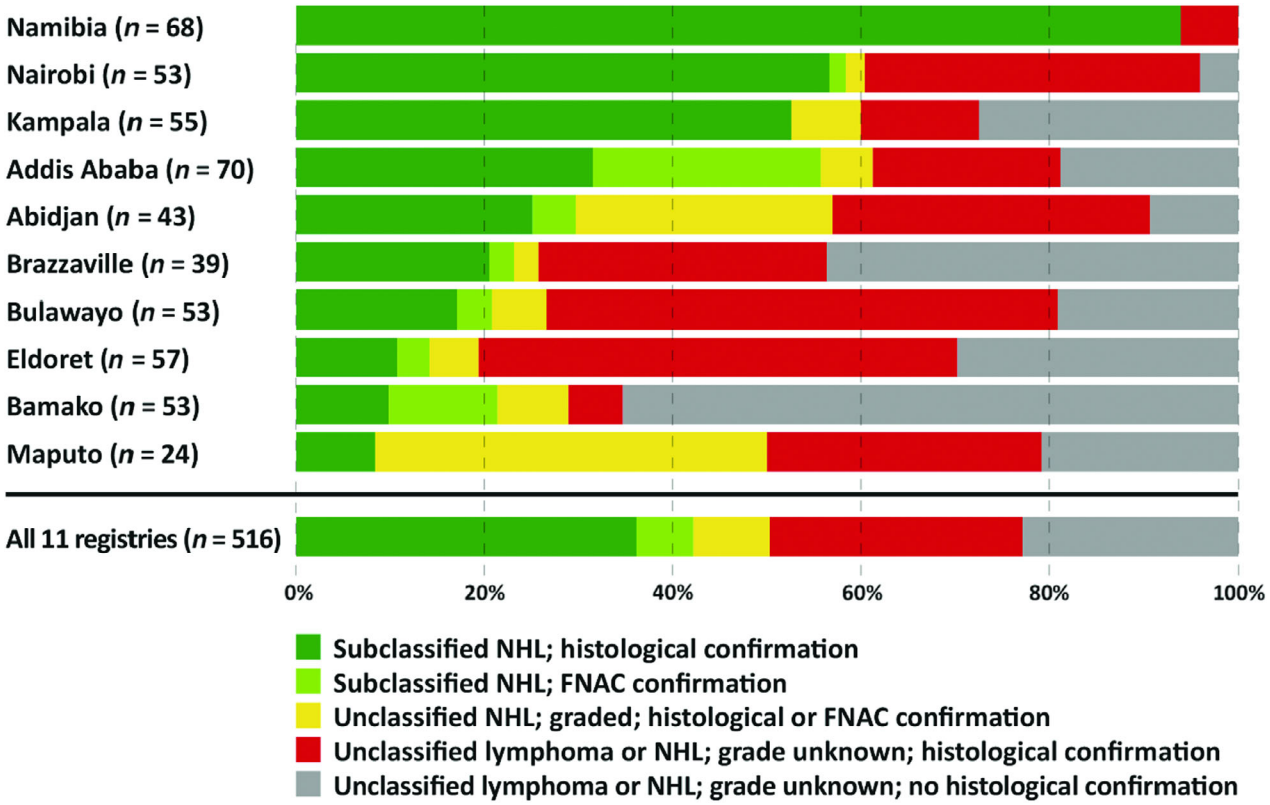


Fig. 3. Quality of pathological diagnosis. Stratified by population-based cancer registries, in order of quality of pathological diagnosis. With respect to non-Hodgkin lymphoma (NHL) subclassification, grade and diagnostic modality [according to National Comprehensive Cancer Network guidelines harmonised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

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

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

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

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

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

Table III. Demographics, diagnostic modality and clinical presentation.

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

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

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

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

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

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

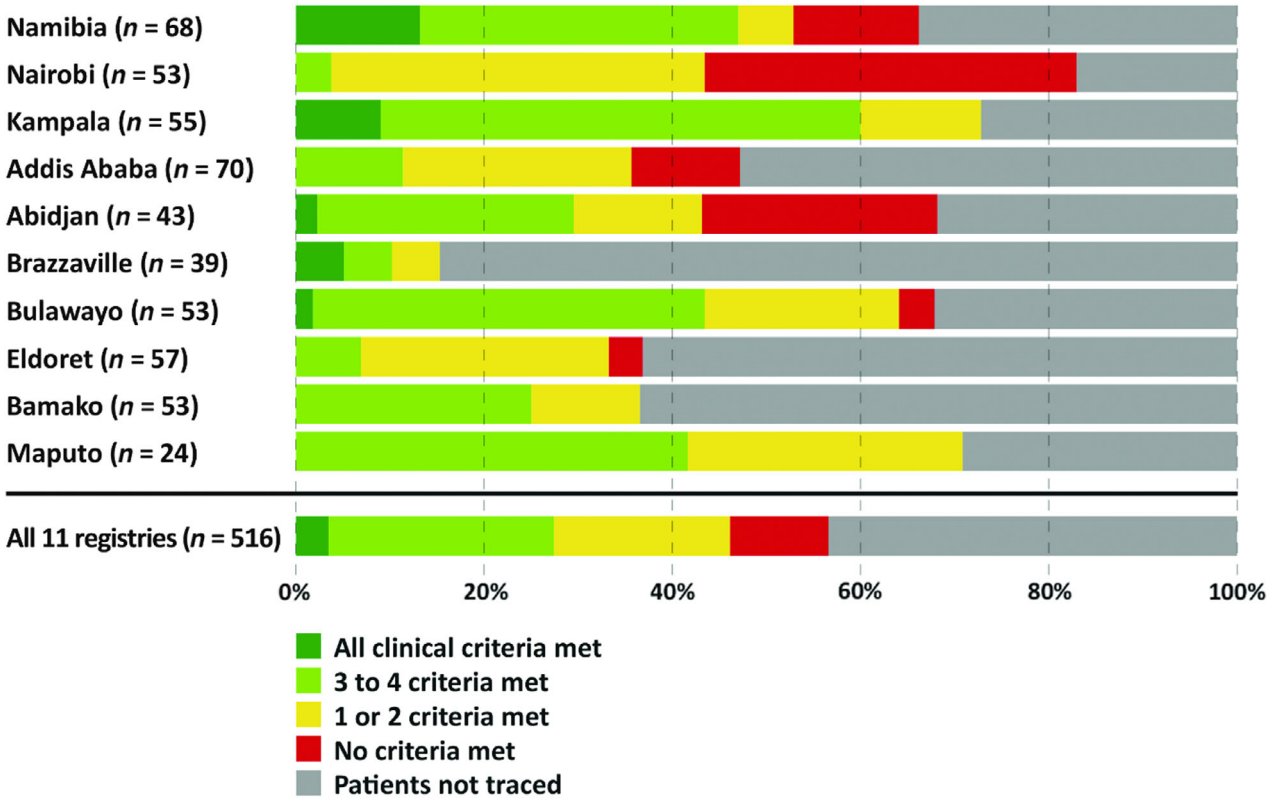


Fig. 4. Completeness of clinical diagnostic criteria. Stratified by population-based cancer registries, in order of Figure 3. With respect to information on Eastern Cooperative Oncology Group Performance Status, B symptoms, human immunodeficiency virus status, stage and any imaging [according to National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

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

Discussion

Unclassified lymphoma cases and diagnostic modality

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

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

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

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

Subtypes of non-Hodgkin lymphoma

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

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

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

Clinical presentation

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

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

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

Strengths and limitations of our study

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

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

Conclusion

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

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Author contributions

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

Conflicts of interest

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

Supporting Information

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

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

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

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

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

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

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

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Original Article

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

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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

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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

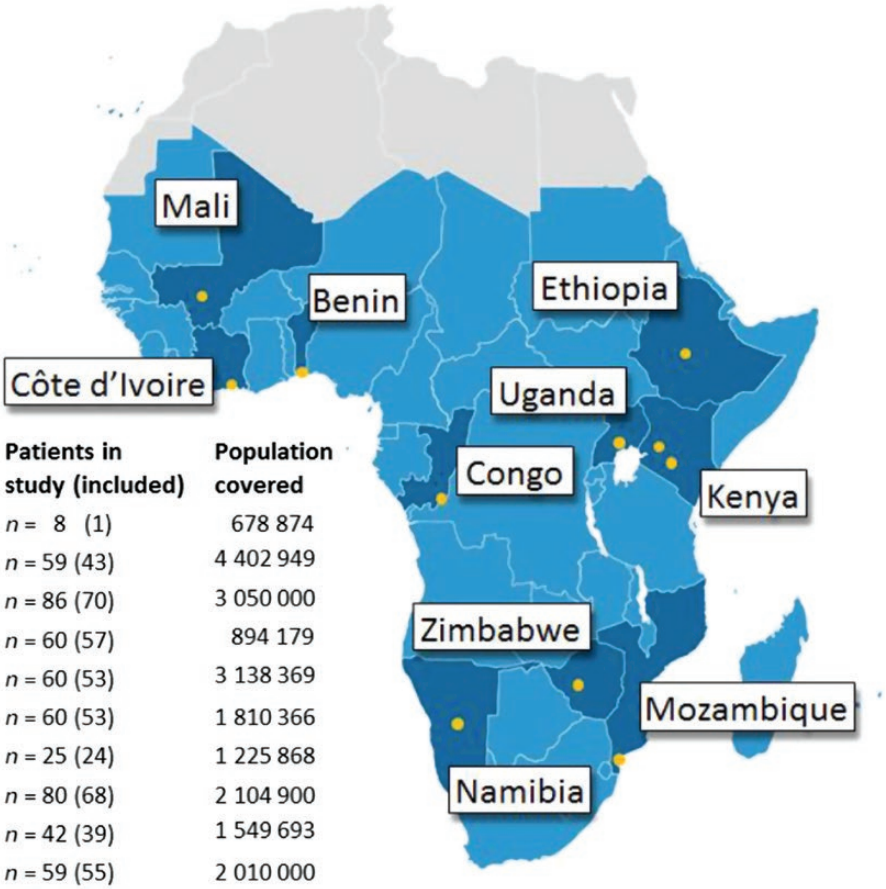
In 2014, AFCRN coordinated 23 regional population-based cancer registries (PBCRs) as International Agency for Research on Cancer's regional hub in SSA.[23] Of these, 11 registries in 10 countries consented to serve as study centers, covering a population of roughly 21.5 million (Fig. 1). We included 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).

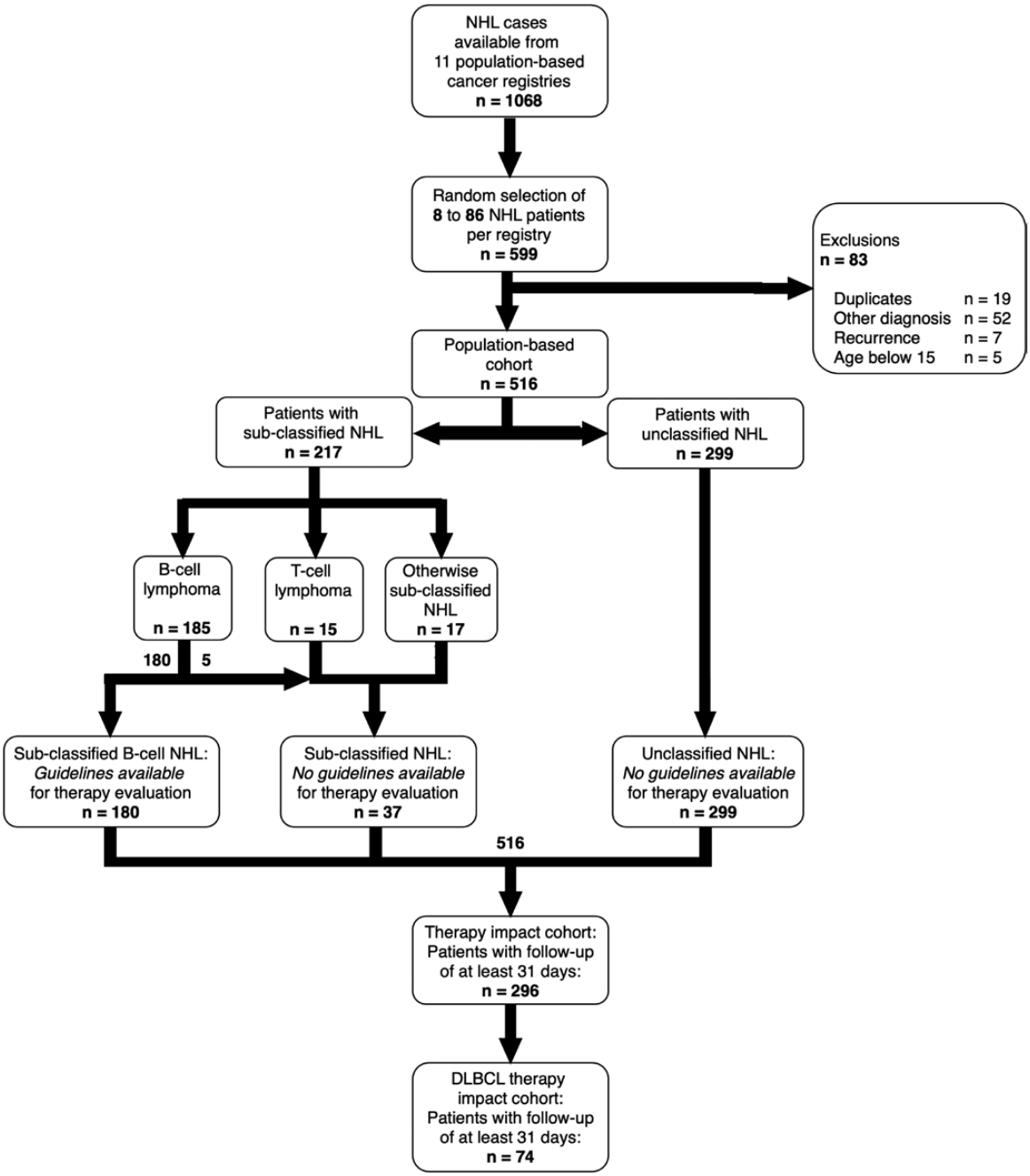


Figure 2. Flow chart of the study population. NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma.

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.

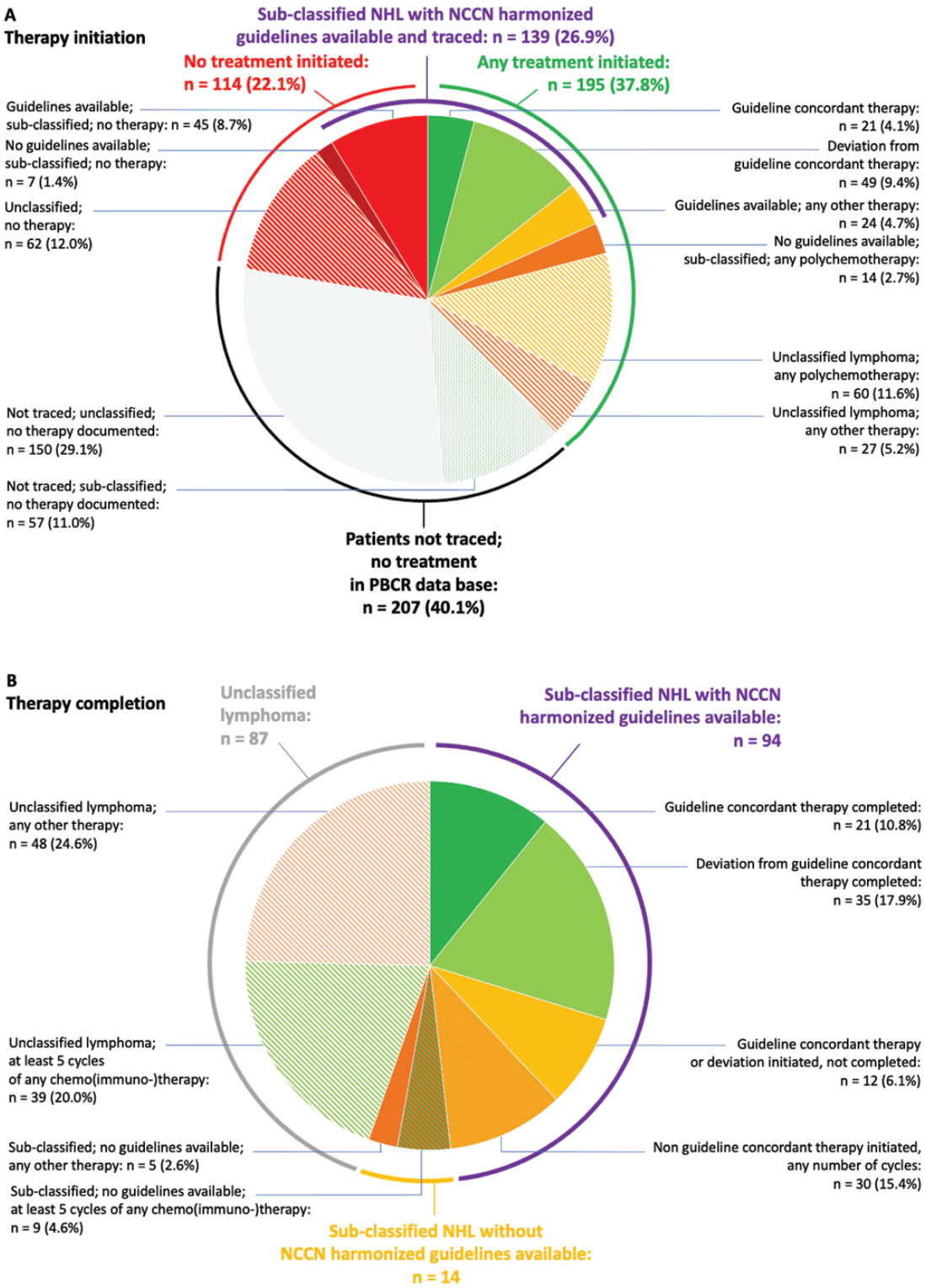


Figure 3. Evaluation of guideline concordance. (**A**) Depicts evaluation of therapy *initiation* in the population-based cohort (n = 516). Percentages refer to the proportion of all patients in cohort. (**B**) Depicts evaluation of therapy *completion* in all patients with any treatment documented (n = 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.

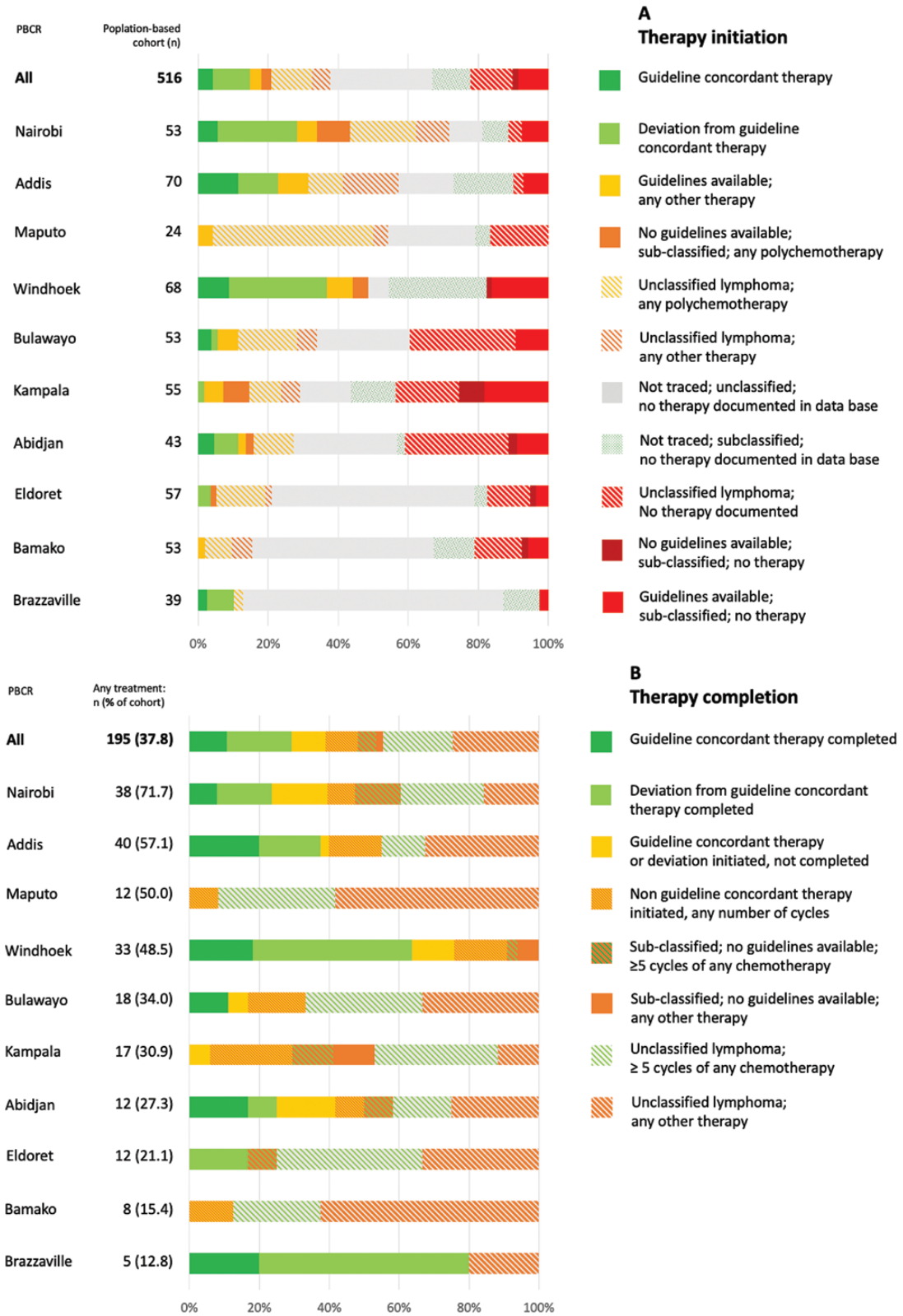


Figure 4. Stratification of evaluation of guideline concordance by population-based cancer registries. (**A**) Depicts evaluation of therapy *initiation* within the population-based cohort (n = 516). Percentages refer to proportion of all patients in respective population-based cancer registries. (**B**) 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.

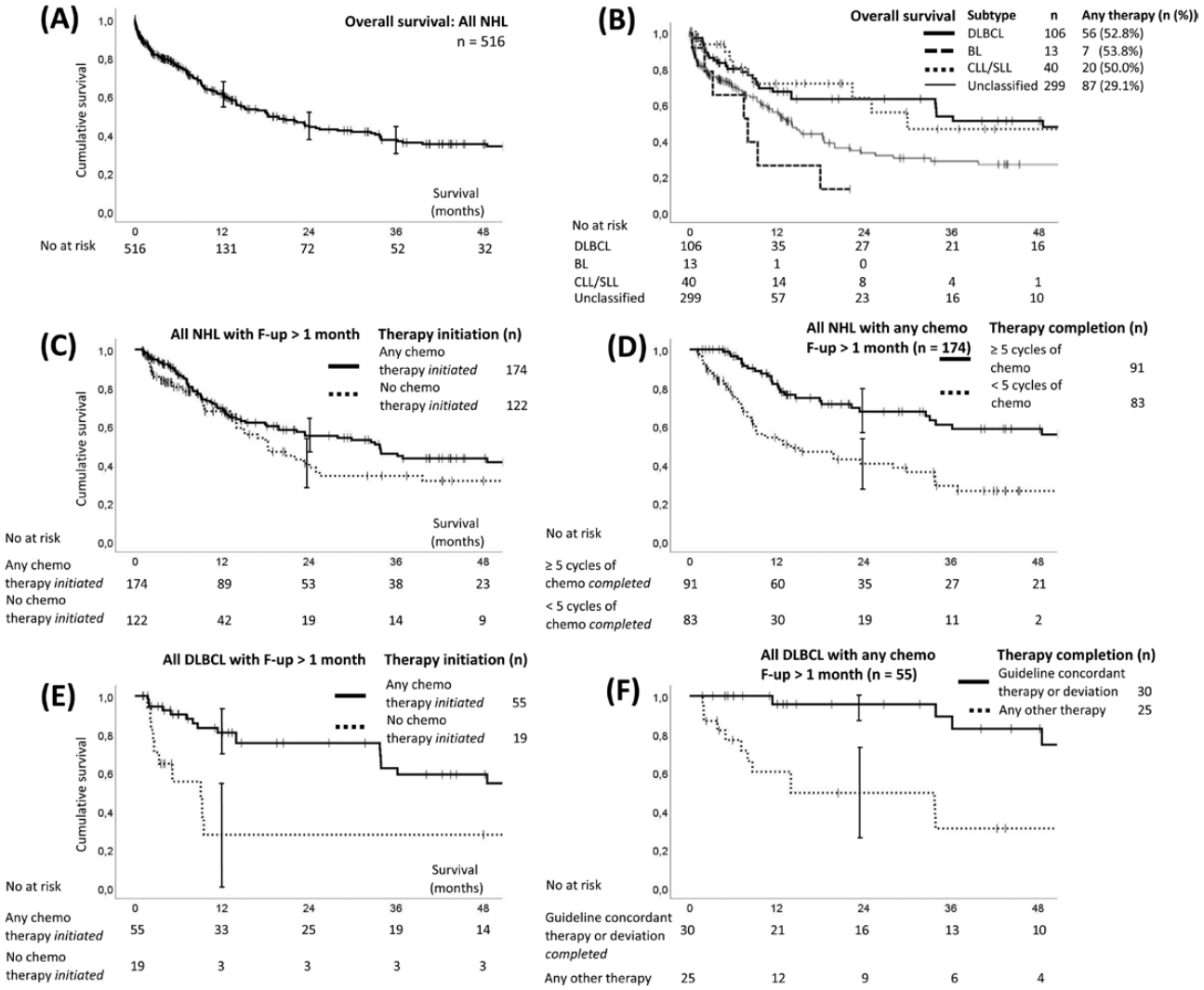


Figure 5. Survival by Kaplan-Meier estimates. (**A**) Overall survival of population-based cohort (n = 516); 95% CI indicated for 12, 24, and 36 months. (**B**) Overall survival of population-based cohort stratified by different subtypes and unclassified lymphoma. (**C**) Survival of population-based 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

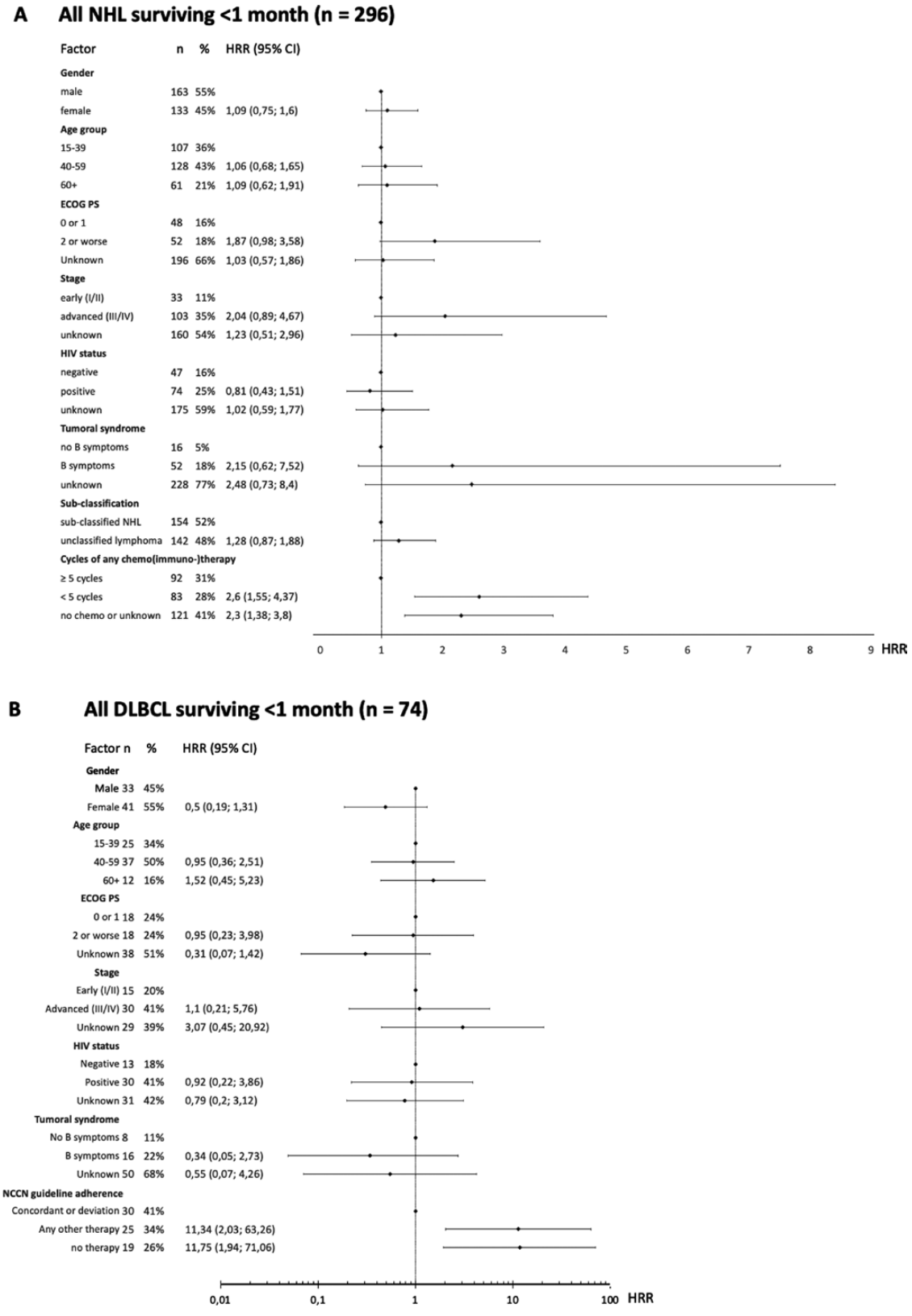


Figure 6. Results of multivariable Cox regression analysis for risk of early death. **A:** All NHL in the population-based cohort with at least 1 month of survival (*n* = 296). **B:** All DLBCL in the population-based cohort with at least 1 month of survival (*n* = 74). HRR, hazard rate ratio.

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.

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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.

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Global Health and Cancer

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

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

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

Abstract

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

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

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

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

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

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

Introduction

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

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

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

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

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

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

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

Materials and Methods

Study Design

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

Sources of Data and Study Population

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

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

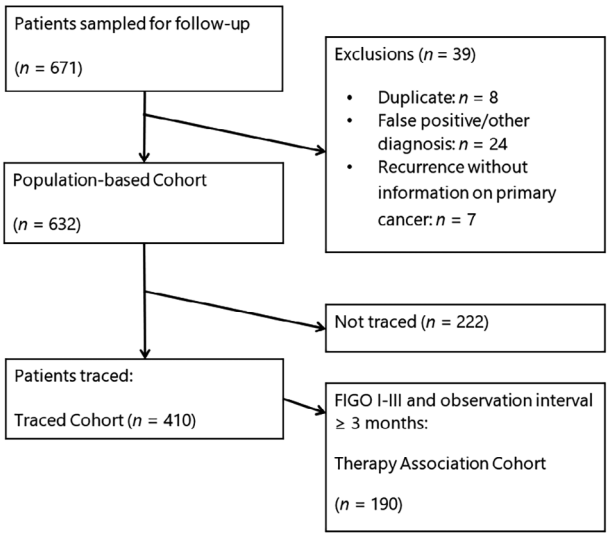

Figure 1. Trial flow diagram. Patients with hospital files found or successful telephone contact were considered to be traced. Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

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

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

Therapy Evaluation

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

Outcome

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

Statistical Methods

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

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

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

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

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

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

Ethics

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

Results

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

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

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

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

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

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

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

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

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

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

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

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

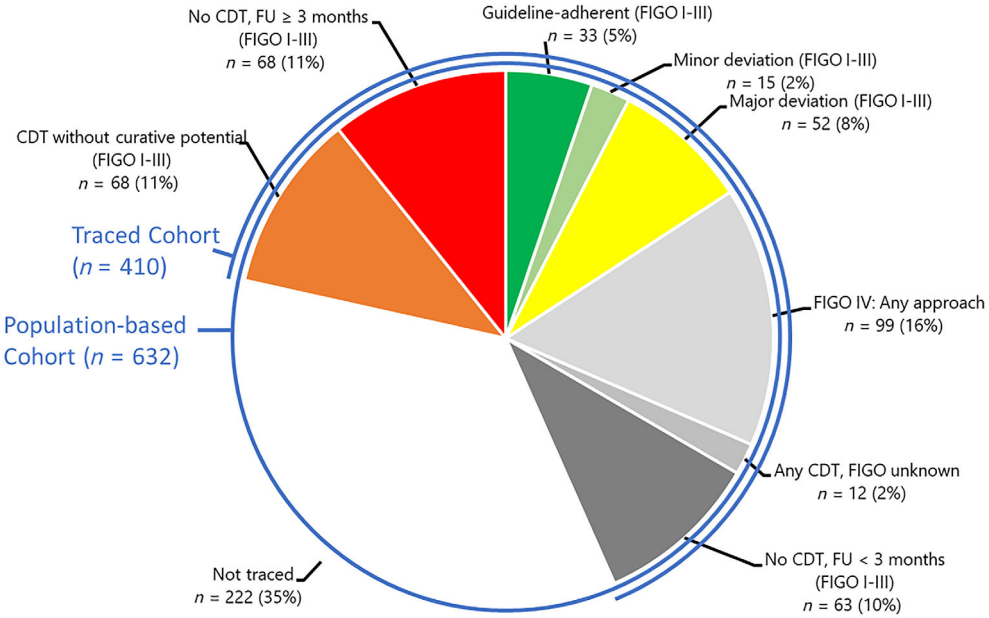

Figure 2. Therapy evaluation in the population-based cohort (*n* = 632). Evaluations refer to the therapy evaluation scheme in Table 1. Colors depict the degree of adherence: green indicates optimal, light green minor deviation, yellow major deviation, orange CDT without curative potential, and red no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

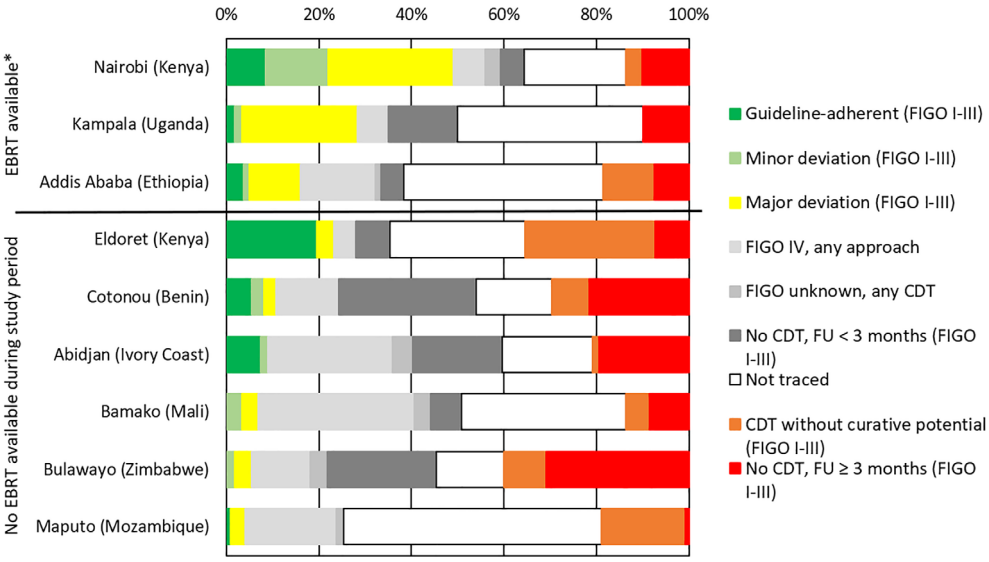

Figure 3. Therapy evaluation in the population-based cohort (*n* = 632) stratified by registry. Evaluations refer to the therapy evaluation scheme in Table 1. Colors depict the degree of adherence: green indicates optimal, light green minor deviation, yellow major deviation, orange CDT without curative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

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

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

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

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

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

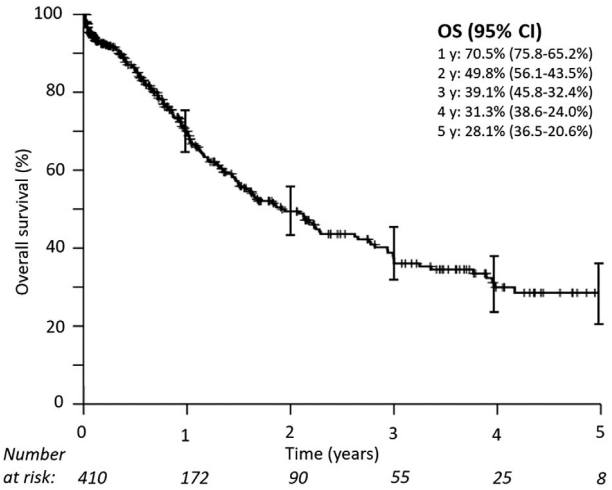

Figure 4. Overall survival in the traced cohort ($n = 410$). Median overall survival was 23 months. Patients with hospital files found or successful telephone contact were considered to be traced.
Abbreviations: CI, confidence interval; OS, overall survival.

Discussion

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

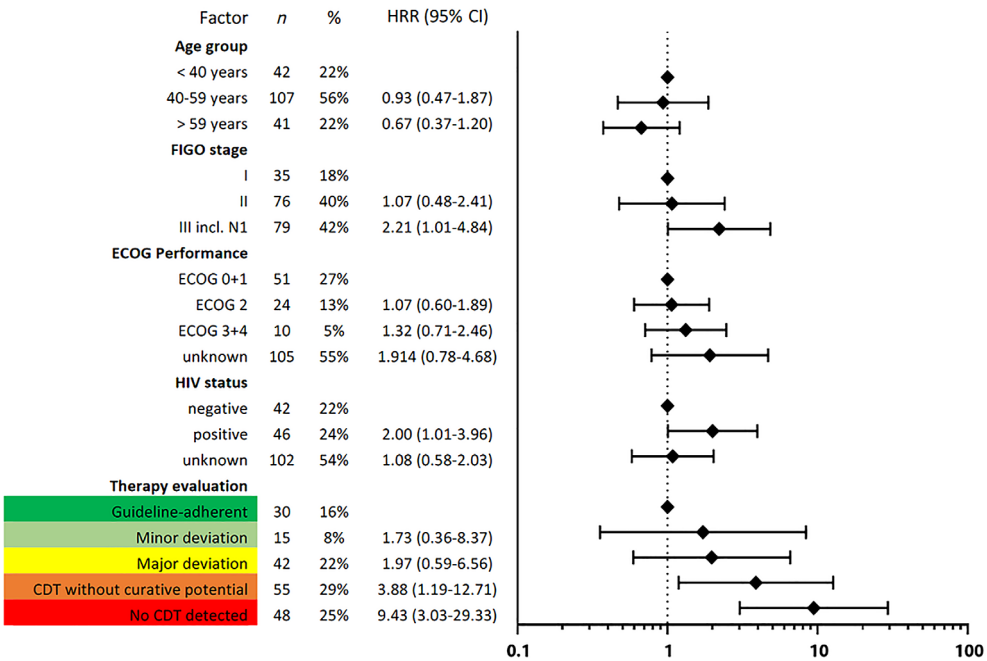

Figure 5. Results of multiple Cox regression for risk of early death in the therapy association cohort ($n = 190$) are shown: through inclusion criteria (FIGO stages I–III and follow-up ≥3 months), bias was reduced. Therapy evaluation refers to Table 1.
Abbreviations: CDT, cancer-directed therapy; CI,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

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

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

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

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

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

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

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

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

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

Conclusion

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

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Disclosures

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

Original Article

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

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

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

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See editorial on pages 4131-4132, this issue.

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INTRODUCTION

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

g patients' survival.[11,12]

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

MATERIALS AND METHODS

Study Design and Data Source

In our longitudinal, population-based, observational registry study, we assembled information from 11 population-based cancer registries (PBCRs) in 10 SSA countries (Fig. 1). We collected data on the presentation, diagnostic workup, patterns of care, and factors influencing survival of patients diagnosed with PCa between 2010 and 2015. The participating PBCRs included the Registre des Cancers d'Abidjan (Côte D'Ivoire), the Addis Ababa City Cancer Registry (Ethiopia), the Registre des Cancers du Mali (Bamako, Mali), the Registre des Cancers de Brazzaville (Congo), the Bulawayo Cancer Registry (Zimbabwe), the Cotonou Cancer Registry (Benin), the Eldoret Cancer Registry (Kenya), the Kampala Cancer Registry (Uganda), the Maputo Cancer Registry (Mozambique), the Nairobi Cancer Registry (Kenya), and the Namibian National Cancer Registry. All these registries are members of the African Cancer Registry Network (AFCRN), the African regional hub for the Global Initiative for Cancer Registry Development of the International Agency for Research on Cancer. Among the 31 AFCRN member registries from 21 countries in 2016 invited to participate in the study, the 11 aforementioned registries consented to participate in the study. The AFCRN research committee (March 2, 2016) and the respective registries' responsible bodies approved this study a priori. The PBCRs covered populations ranging from 653,000 (Bulawayo) to 4.4 million (Abidjan); they summed up to approximately 21.5 million.[1]

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

Data Collection

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

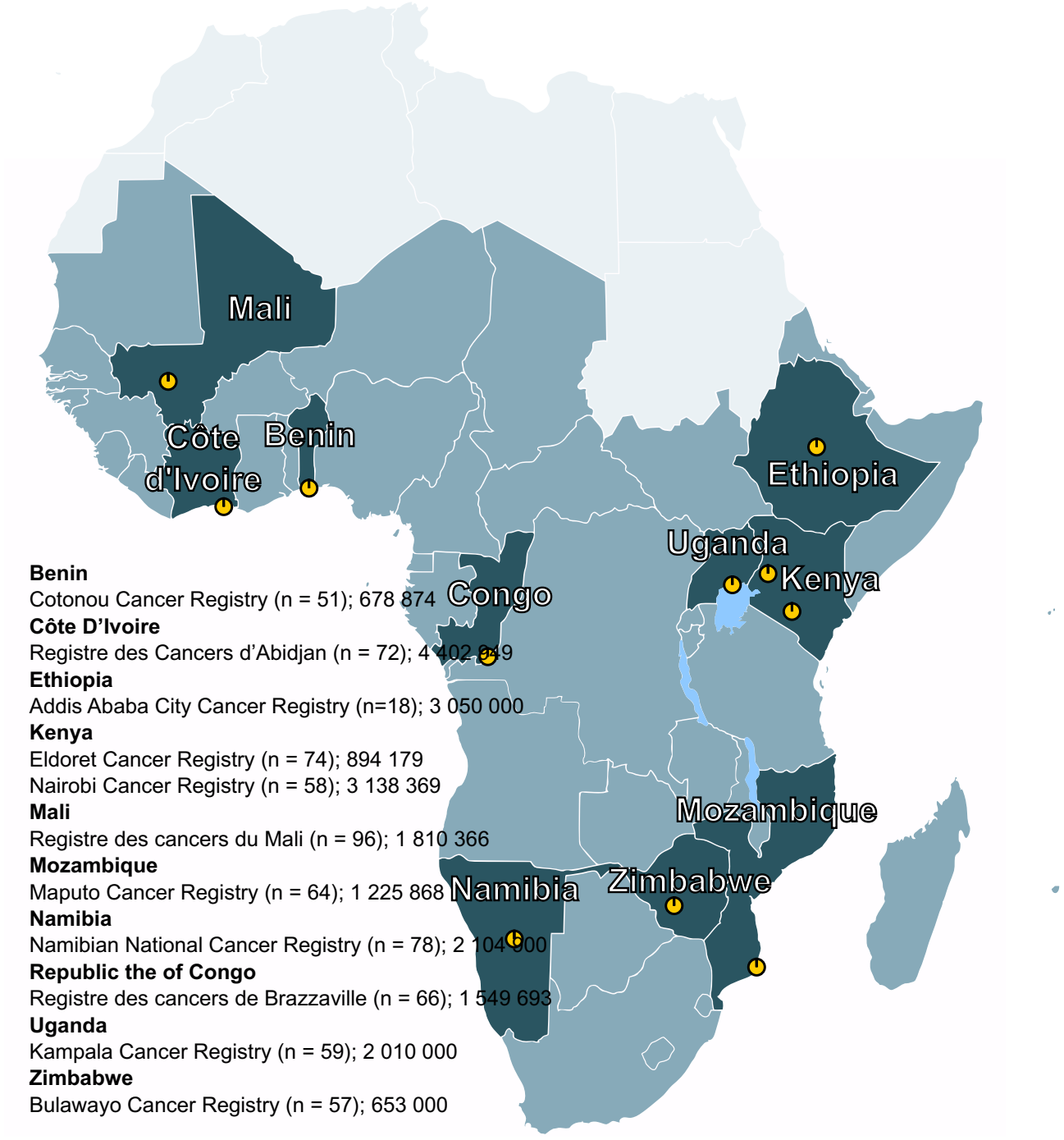

Figure 1. Countries of participating cancer registries. Countries of participating population-based cancer registries are highlighted along with the names of the registries, the number of included patients (n), and the population of each coverage area (persons).

our study included the following: PSA level at diagnosis, Gleason score, physical examination (ie, digital rectal examination [DRE]), imaging methods for staging, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and TNM stage. The types of treatment data included surgery, radiotherapy, and endocrine therapy. We classified these with respect to cancer-directed therapy (CDT): "curative approach" (RP and EBRT with a cumulative dose of at least 60 Gy in nonmetastatic patients), "any other approach with ADT" (ADT monotherapy or

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

Statistical Analysis

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

RESULTS

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

Patient Characteristics and Diagnostic Workup

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

Primary Treatment Approach

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

TABLE 1. Patient Characteristics

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

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

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

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

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

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

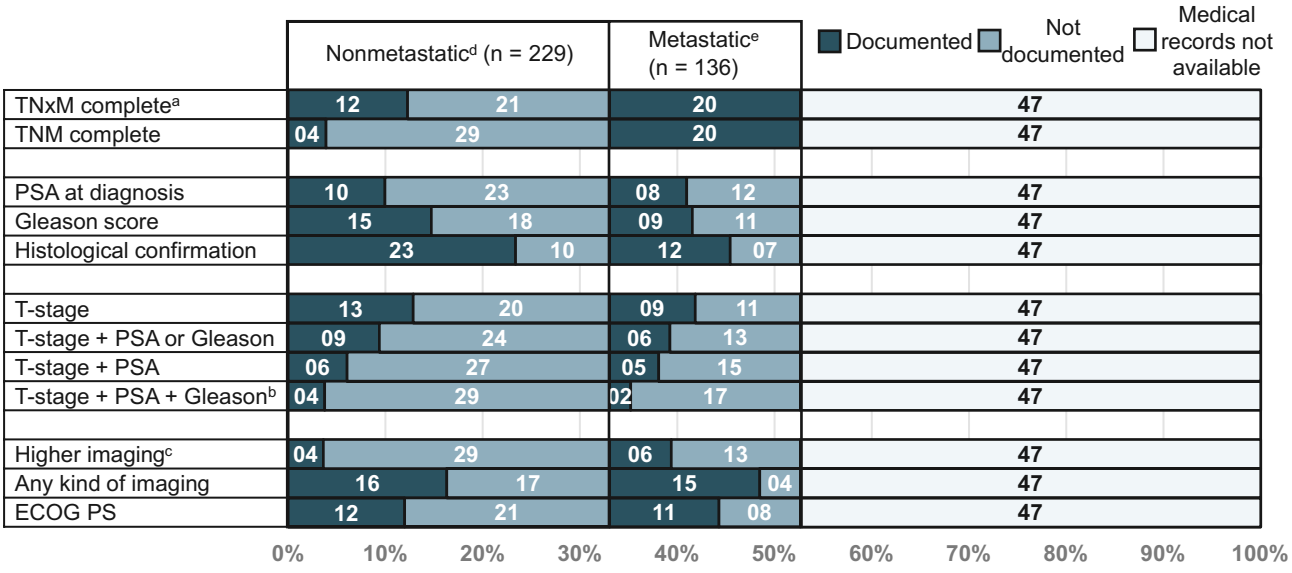

Figure 2. Availability of diagnostic information for patients with prostate cancer in the total population-based cohort (n = 693). [a]Nx included. [b]Main prognostic factors according to the 2017 National Comprehensive Cancer Network guidelines. [c]For example, computed tomography, magnetic resonance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

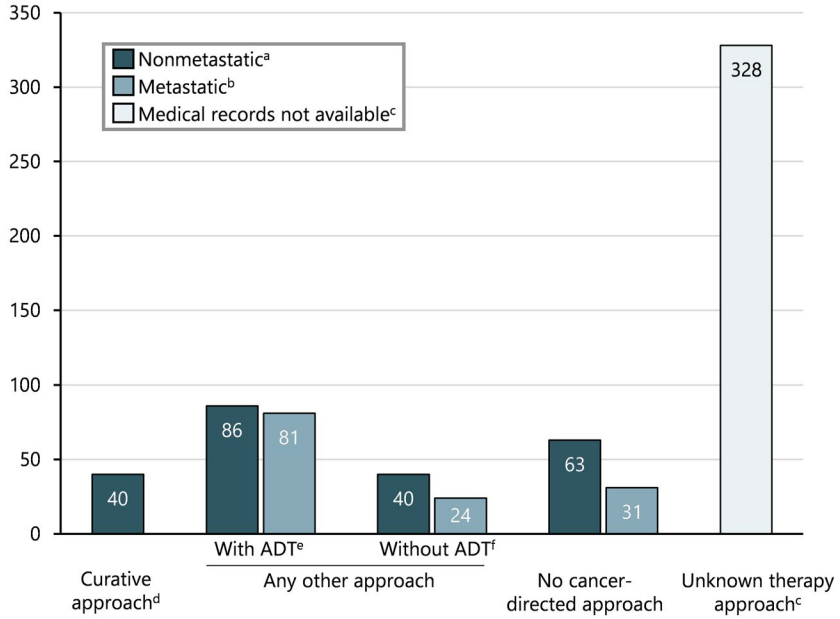

Figure 3. Primary treatment approach by identified M stage in the total population-based cohort (n = 693). [a]The nonmetastatic subgroup (n = 229) comprised all patients without a pathological or clinical suggestion of metastasis (M0), including patients with an unknown lymph node status (Nx M0). [b]The metastatic subgroup (n = 136) comprised all patients with a pathological or clinical suggestion of metastasis (M1), including all patients with a positive lymph node status (N1). [c]No medical records were available for the extraction of clinical data (n = 328). [d]Radical prostatectomy or external-beam radiation therapy with a potentially curative dose. [e]ADT monotherapy by surgical or medical castration or ADT by surgical or medical castration in combination with transurethral resection of the prostate or external-beam radiation therapy with a palliative dose or chemotherapy. [f]Transurethral resection of the prostate or external-beam radiation therapy with a palliative dose or chemotherapy without ADT. ADT indicates androgen deprivation therapy.

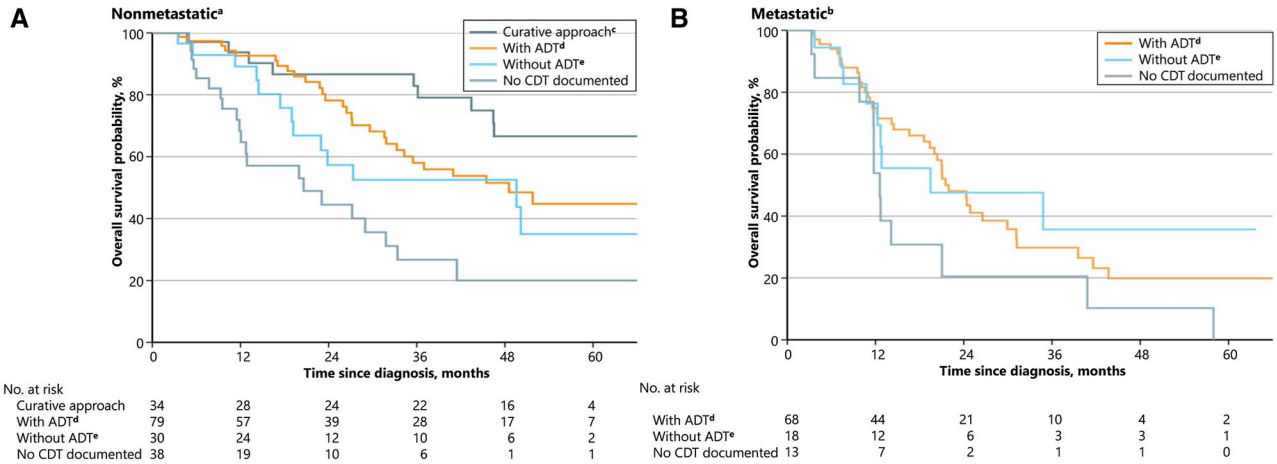

Figure 4. Overall survival of patients from the traced cohort with at least 3 months of survival stratified by M stage: differences according to the treatment approach. [a]These patients surviving at least 3 months from the nonmetastatic subgroup (n = 181) included all patients without a pathological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

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

Survival Analysis

In our total cohort (n = 693), survival data were available for 491 patients (183 deaths during observation; median follow-up, 9.3 months). The observed 1-, 3-, and 5-year OS rates were 73.3% (95% CI, 68.6%-78.0%), 42.6% (95% CI, 36.3%-48.9%), and 31.2% (95% CI, 24.5%-37.9%), respectively. The observed OS varied among the different PBCR areas (Supporting Fig. 2). The 1-, 3-, and 5-year ASRS was 82.2% (95% CI, 76.0%-86.9%), 58.8% (95% CI, 48.5%-67.7%), and 56.9% (95% CI, 39.8%-70.9%), respectively (Supporting Table 4A). When we looked at the outcomes of the traced cohort (n = 365) stratified by M stage, the observed 1-, 3-, and 5-year OS rates for the nonmetastatic subgroup (n = 229) were 82.8% (95% CI, 77.3%-88.4%), 53.7% (95% CI, 45.5%-61.9%), and 41.1% (95% CI, 32.1%-50.2%), respectively (Supporting Table 4B). For the metastatic subgroup (n = 136), they were 61.2% (95% CI, 52.2%-70.2%), 25.8% (95% CI, 16.4%-35.2%), and 14.7% (95% CI, 5.0%-24.5%), respectively. In the Kaplan-Meier analysis of patients in the traced cohort surviving at least 3 months (n = 280), who were stratified as nonmetastatic or metastatic, we found OS differences between management approaches: in this subgroup, nonmetastatic patients (n = 181) with curative- and noncurative-treatment approaches had better OS than patients with no CDT documented (Fig. 4A). Metastatic patients (n = 99) with any form of treatment approach had better OS than patients with no CDT documented (Fig. 4B).

Multivariable Analysis

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

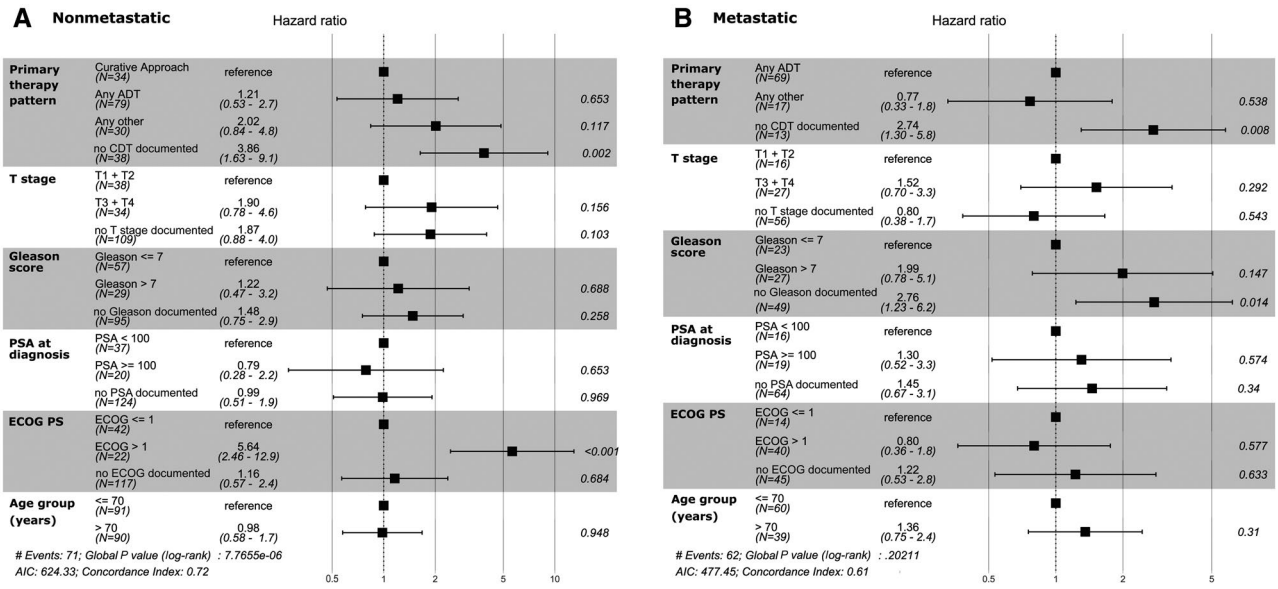

Figure 5. Forest plots showing the influence of primary treatment patterns on the survival of (A) patients with nonmetastatic prostate cancer[a] and (B) patients with metastatic prostate cancer.[b] The hazard ratios and 95% confidence intervals are the results of a multivariable Cox regression model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

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

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

DISCUSSION

This study is, to our knowledge, the first to assess the status of diagnostics, treatments, and outcomes in a random sample of population-based patients with PCa from SSA. We found that patients with PCa presented at a late stage and lacked adequate diagnostic workup and treatment, and this led to unfavorable outcomes. A complete diagnostic workup for risk stratification, including the tumor stage, Gleason score, and PSA level, was documented for only 11% of the traced cohort (n = 365). We found that less than one-fifth of the nonmetastatic subgroup (n = 229) received therapy with curative intent. Nearly two-fifths of our traced cohort (n = 365) were diagnosed with metastatic disease. In this metastatic subgroup (n = 136), only two-thirds received ADT. In a multivariable analysis, a lack of CDT for nonmetastatic and metastatic patients was strongly associated with a higher risk of mortality.

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

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

There are different treatment approaches to be considered according to the risk group, life expectancy, and patients' preferences. International guidelines propose a curative approach for all symptomatic, nonmetastatic patients.[11,12] The low proportion of curative-treatment approaches in our population-based cohort was also seen in previous hospital-based studies in SSA. For example, only 0% and 12% of patients with PCa from Nigeria and South Africa, respectively, were managed with a curative-treatment approach.[25,26] At the national radiotherapy center in Ghana, 56% of patients with nonmetastatic PCa received curative radiotherapy.[27] In our subgroup of patients with nonmetastatic PCa, 82% did not receive curative therapy, and more than 1 in 3 patients received ADT only without RP or EBRT. Reasons for the low proportion of curative-intent treatment in our study may include a lack of specialized surgeons/urologists in the region to perform adequate RP.[28] Furthermore, a lack of radiotherapy machines is a major barrier to the receipt of radiotherapy in the region[18,29] (Supporting Table 6). In contrast to our findings of relatively frequent use of ADT for nonmetastatic patients, international guidelines do not recommend the use of ADT as monotherapy for symptomatic, nonmetastatic PCa because studies have shown that the addition of adequate local therapy options improves survival significantly.[11,12] Nevertheless, in a low-resource setting and in the absence of more adequate CDT, substandard care such as bilateral orchiectomy for symptomatic nonmetastatic disease is an economically viable treatment option and may extend patients' survival and improve their quality of life.[30]

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

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

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

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

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

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

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

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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 cancer-directed 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.

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Abstract

Background: The burden of colorectal cancer (CRC) is increasing in Sub-Saharan Africa (SSA). However, little is known about CRC treatment and survival in the region.

Methods: A random sample of 653 patients with CRC diagnosed from 2011 to 2015 was obtained from 11 population-based cancer registries in SSA. Information on clinical characteristics, treatment, and/or vital status was obtained from medical records in treating hospitals for 356 (54%) of the patients ("traced cohort"). Concordance of CRC treatment with NCCN Harmonized Guidelines for SSA was assessed. A Cox proportional hazards model was used to examine the association between survival and human development index (HDI).

Results: Of the 356 traced patients with CRC, 51.7% were male, 52.8% were from countries with a low HDI, 55.1% had colon cancer, and 73.6% were diagnosed with nonmetastatic (M0) disease. Among the patients with M0 disease, however, only 3.1% received guideline-concordant treatment, 20.6% received treatment with minor deviations, 31.7% received treatment with major deviations, and 35.1% received no treatment. The risk of death in patients who received no cancer-directed therapy was 3.49 (95% CI, 1.83-6.66) times higher than in patients who received standard treatment or treatment with minor deviations. Similarly, the risk of death in patients from countries with a low HDI was 1.67 (95% CI, 1.07-2.62) times higher than in those from countries with a medium HDI. Overall survival at 1 and 3 years was 70.9% (95% CI, 65.5%-76.3%) and 45.3% (95% CI, 38.9%-51.7%), respectively.

Conclusions: Fewer than 1 in 20 patients diagnosed with potentially curable CRC received standard of care in SSA, reinforcing the need to improve healthcare infrastructure, including the oncology and surgical workforce.