Präsentation, Therapie und Überleben von Patientinnen mit Zervixkarzinom in Äthiopien 2008-2012

Dissertation zur Erlangung des akademischen Grades

Doktor der Medizin (Dr. med.)

vorgelegt

der Medizinischen Fakultät der

Martin-Luther-Universität Halle-Wittenberg

von Matthias Begoihn

Betreuerin: Prof. Dr. med. Eva Kantelhardt

Gutachter*innen:

Herr Prof. Dr. Christoph Thomssen (Halle)

Frau Prof. Dr. Stefanie J. Klug (München)

Datum der Verteidigung: 04.12.2023

Referat

Das Zervixkarzinom ist einer der häufigsten Tumoren der Frau in Äthiopien. Wir analysierten eine retrospektive Krankenhauskohorte von über 1500 Patientinnen mit histologisch nachgewiesenem, invasivem Zervixkarzinom in Addis Abeba, Äthiopien. Die Patientinnen stellten sich in einem Vierjahreszeitraum zwischen dem 10.09.2008 und dem 10.09.2012 im Tikur Anbessa Hospital – dem einzigen Strahlentherapiezentrum des Landes – vor. Diese Kohorte dient als Stichprobe für die erste großangelegte Studie in Subsahara-Afrika, welche Patientinnencharakteristika, Wartezeiten bis zur Diagnose und Therapie, das Gesamtüberleben sowie Nebenwirkungen der Therapie untersucht. Nahezu alle Patientinnen wurden mit bereits symptomatischer Erkrankung diagnostiziert. Wir beobachteten lange Zeiträume zwischen dem ersten Symptombeginn und der histologischen Diagnose, welche im Median 30 Wochen betrugen. Lange Zeiträume bis zur Diagnosestellung waren mit höheren Tumorstadien assoziiert, welche einen wichtigen Prognosefaktor darstellen. Insbesondere bei Frauen aus ländlichen Regionen vergingen längere Zeiträume bis zur Diagnose. Auch ein positiver HIV-Status war mit weiter fortgeschrittenen Tumorstadien zum Diagnosezeitpunkt assoziiert. Patientinnen mit positivem HIV-Status waren im Mittel 10 Jahre jünger als solche mit negativem oder unbekanntem HIV-Status. Ein Großteil der Patientinnen stellte sich in fortgeschrittenen Tumorstadien im Tikur Anbessa Hospital vor, weshalb eine kurative Therapie in diesen Fällen nicht möglich und mit einem ungünstigen Gesamtüberleben assoziiert war. Während langer Wartezeiten bis zum Therapiebeginn vergrößerte sich der Anteil von Patientinnen mit weit fortgeschrittenem Tumorstadium. Patientinnen mit Zervixkarzinom warteten im Median 2,1 Monate auf eine Operation während bis zum Beginn der Bestrahlung im Median ganze 3,8 Monate vergingen. Patientinnen mit unvollständiger Bestrahlungstherapie wiesen ein schlechteres Gesamtüberleben im Vergleich zu Patientinnen mit vollständiger Bestrahlungstherapie auf. Trotz eindeutig belegtem Nutzen einer kombinierten Radiochemotherapie erhielten nur 17 % der Patientinnen eine Chemotherapie. Diese Arbeit verdeutlicht, dass Maßnahmen notwendig sind, um die lange Zeit zwischen Symptombeginn und Diagnosestellung sowie bis zum Beginn der Therapie zu reduzieren. Um Wartezeiten zu verkürzen, müssen Diagnostik und Therapie weiter auch auf ländliche Regionen ausgedehnt werden. HIV-Patientinnen stellen eine Hochrisikogruppe für die Entwicklung eines Zervixkarzinoms dar. Bestehende Infrastruktur für die HIV-Therapie sollte zur Prävention und Früherkennung des Zervixkarzinoms genutzt werden.

Begoihn, Matthias: Präsentation, Therapie und Überleben von Patientinnen mit Zervixkarzinom in Äthiopien 2008-2012, Halle (Saale), Univ., Med. Fak., Diss., 60 Seiten, 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

AIDS	Akquiriertes Immun-Defizienz-Syndrom
ART	Antiretrovirale Therapie
CD4	Cluster der Differenzierung 4
CIN	Zervikale intraepitheliale Neoplasie
FIGO	Internationale Föderation für Gynäkologie und Geburtshilfe
HIC	Länder mit hohem Einkommen
HIV	Humanes Immundefizienz-Virus
HPV	Humanes Papillomavirus
LMIC	Länder mit niedrigem und mittlerem Einkommen
R	Resektionsrand
T	Tumorgröße
WHO	Weltgesundheitsorganisation

Das Zervixkarzinom – ein weltweit ungleich erfahrenes Gesundheitsproblem

1. Einleitung und Zielstellung

Während in Ländern des globalen Nordens immer weniger Frauen am Zervixkarzinom erkranken und versterben, ist die Erkrankung in Ländern mit niedrigem und mittlerem Einkommen (LMIC) noch immer ein zentrales Gesundheitsproblem. In diesen Ländern ist das Zervixkarzinom der zweithäufigste Tumor der Frau und derjenige mit der zweithöchsten Mortalität. So starben im Jahr 2020 nach Erhebungen der Global Cancer Statistics weltweit 342.000 Frauen am Zervixkarzinom – davon nahezu 90 % in LMICs (1). Diese Diskrepanz zwischen Ländern mit hohem Einkommen (HIC) gegenüber LMICs spiegelt eine große Ungleichheit in Bezug auf den Zugang und die Qualität medizinischer Versorgung wider (2).

In HICs gehört es mittlerweile zum Standard, regelmäßige gynäkologische Untersuchungen mit Abstrichen der Cervix Uteri zur zytologischen Untersuchung und gegebenenfalls HPV-Testung durchzuführen. So konnte in HICs in den letzten dreißig Jahren seit Einführung umfangreicher Screeningmaßnahmen die Inzidenz und Mortalität des Zervixkarzinoms mehr als halbiert werden (3). Denn das Zervixkarzinom ist eine durch Impfung und Screeningmaßnahmen vermeidbare sowie – frühzeitig diagnostiziert und behandelt – heilbare Erkrankung.

Aus der Gruppe der LMICs sind Frauen in Subsahara-Afrika in besonderem Maße durch das Zervixkarzinom betroffen. Hier liegen die Inzidenz- und Mortalitätsraten deutlich über dem weltweiten Durchschnitt aufgrund mangelnder Verfügbarkeit präventiver, diagnostischer und therapeutischer Maßnahmen (4,5). In diesen Ländern erfolgt die Diagnose aufgrund fehlender Screeningmaßnahmen häufig erst nach Auftreten von Symptomen wie vaginaler Blutung, vaginalem Ausfluss oder abdominellen Schmerzen. Zu diesem Zeitpunkt ist der Tumor jedoch meist in einem bereits fortgeschrittenen Stadium, sodass eine kurative Behandlung oft nicht möglich und die Prognose schlecht ist (6,7).

In Äthiopien ist das Zervixkarzinom nach dem Mammakarzinom der Tumor mit der zweithöchsten Inzidenz und Mortalität bei Frauen (1). Fast 80 % der äthiopischen Bevölkerung lebt in ländlichen Regionen, in denen der Zugang zu qualitativ hochwertiger medizinischer Versorgung häufig mangelhaft ist (8). Laut qualitativen Erhebungen der äthiopischen Regierung aus dem Jahr 2016 erhalten insbesondere Frauen keine (48 %) oder lediglich eine unvollständige Grundschulbildung (32 %). Äthiopische Frauen beginnen ihre sexuelle Aktivität mit durchschnittlich 16,6 Jahren, heiraten mit 17 Jahren und haben im Schnitt fünf Kinder.

Außerdem berichtete etwa jede zehnte befragte Frau, dass ihr Ehemann mehrere Ehefrauen habe (9). Diese sozioökonomischen Strukturen machen Frauen in Äthiopien besonders vulnerabel für die Entwicklung sexuell übertragbarer Erkrankungen.

Neben Infektionskrankheiten wie HIV/AIDS, Tuberkulose und Malaria, deren Inzidenz- und Mortalitätsraten in der jüngeren Vergangenheit reduziert werden konnten, tragen Tumorerkrankungen zunehmend zur Mortalität und Morbidität in Äthiopien bei. So erkrankten im Jahr 2020 geschätzt etwa 7445 äthiopische Frauen am Zervixkarzinom und etwa 5338 verstarben an dem Tumor (1).

Es gilt als gesichert, dass nahezu alle Zervixkarzinome auf dem Boden einer chronischen Infektion mit einem onkogenen Stamm eines humanen Papillomavirus (HPV) entstehen (10). Eine HIV-Infektion, Multiparität, der frühe Beginn sexueller Aktivität, multiple Sexualpartner sowie Rauchen stellen weitere Risikofaktoren dar (11). Durch Persistenz der HPV-Infektion entsteht eine Präkanzerose – eine sogenannte cervikale intraepitheliale Neoplasie (CIN) – aus der sich in einer Latenzzeit von mehreren Jahren bis Jahrzehnten ein invasives Zervixkarzinom entwickelt (12). Daher gibt es über Jahre die Möglichkeit der Prävention. Diverse Studien haben gezeigt, dass sich mit kosteneffizienten Mitteln im Bereich der Primär-, Sekundär- und Tertiärprävention deutliche inzidenz- und mortalitätssenkende Effekte erzielen lassen (13–17). So startete die Weltgesundheitsorganisation (WHO) im Jahr 2019 eine Kampagne mit dem Ziel, das Zervixkarzinom in den nächsten 100 Jahren zu eliminieren (18). Um die dafür benötigte Reduktion der weltweiten Inzidenz von aktuell 13.1 auf weniger als 4 Fälle pro 100.000 Frauen zu erreichen, sind laut zweier Modellierungsstudien folgende Maßnahmen notwendig: Eine globale Impfquote gegen onkogene HPV-Stämme von 90 % aller Mädchen und jungen Frauen, ein zweimaliges Zervixkarzinom-Screening von 70 % aller Frauen im Alter von 35-45 Jahre, sowie eine leitliniengerechte Behandlung von 90 % aller Frauen mit invasivem Zervixkarzinom und dessen Vorstufen. Bereits im Jahr 2070 hätten diese Maßnahmen eine Reduktion der Mortalität um 92 % zur Folge, bis 2120 sogar um 99 % (19,20). Neben diesen wichtigen Maßnahmen der Primär- und Sekundärprävention zur Vermeidung der Erkrankung muss sowohl der Zugang als auch die Qualität von Diagnostik und Therapie bereits erkrankter Frauen verbessert werden.

In Äthiopien findet die Behandlung des Zervixkarzinoms beinahe ausschließlich in der Hauptstadt Addis Abeba statt. Hier befindet sich das Universitätsklinikum Tikur Anbessa Hospital mit der im Jahr 2016 einzigen Klinik für Onkologie und Strahlentherapie des Landes sowie den einzigen beiden Bestrahlungsgeräten in ganz Äthiopien. Die Therapie des Zervixkarzinoms nach örtlichen Leitlinien erfolgt in Abhängigkeit des Tumorstadiums nach FIGO (Fédération Internationale de Gynécologie et d'Obstétrique). Zunächst erfolgt klinisch eine bimanuelle Untersuchung.

Bei ausgeprägtem Lokalbefund oder klinischem Verdacht folgt eine abdominelle Ultraschalluntersuchung sowie eine Röntgenthorax-Untersuchung, welche bei Nachweis einer Hydronephrose oder pulmonalen Fernmetastasen zu einer Korrektur des FIGO-Stadiums nach oben führt.

Frühe FIGO-Stadien I-IIa erhielten eine operative Therapie. Einfache Hysterektomien wurden auch in Krankenhäusern außerhalb Addis Abebas durchgeführt. Wertheim-Meigs-Operationen fanden zum Zeitpunkt der Datenerhebung 2012 ausschließlich im Tikur Anbessa Hospital statt. Hier wurden folgende Therapierichtlinien praktiziert: Patientinnen mit einem FIGO-Stadium >IIa sowie initial operierte Patientinnen, bei denen keine R0-Resektion erreicht werden konnte, wurde eine kombinierte Radiochemotherapie empfohlen. Diese setzt sich aus einer perkutanen Strahlentherapie mittels Cobalt-60 Einheit sowie einer Cisplatin basierten Chemotherapie zusammen.

Eine intrakavitäre Brachytherapie, welche höhere Bestrahlungsdosen im Tumorzentrum ermöglicht und dadurch Schäden der benachbarten Gewebe infolge der perkutanen Bestrahlung verringert, war zum Zeitpunkt der Datenerhebung in Äthiopien nicht verfügbar, ist jedoch seit 2018 im Einsatz.

Bei einer Behandlung des Zervixkarzinoms spielen der Zugang zu Diagnostik, der Diagnosezeitpunkt, die Qualität und Adhärenz zur Therapie, sozioökonomische Faktoren sowie Vorerkrankungen eine wichtige Rolle. Einem Behandlungserfolg des Zervixkarzinoms in Äthiopien stehen demnach verschiedene Herausforderungen gegenüber. Um diese Hindernisse herauszuarbeiten, war es zunächst notwendig Informationen über den Verlauf der Erkrankung vom Beginn der Symptome über die histologische Diagnostik bis hin zu den angewandten Therapiemodalitäten, deren Nebenwirkungen sowie dem Therapieerfolg im Sinne des Gesamtüberlebens zu sammeln. Ein Augenmerk lag insbesondere auf der Länge der Zeiträume zwischen Beginn der ersten Symptome, der histologischen Diagnose sowie dem Beginn der Therapie und deren Einfluss auf Tumorstadium und Gesamtüberleben.

So konnten wir in einer retrospektiven Datensammlung im Jahr 2012 am Tikur Anbessa Hospital Informationen über 1655 Frauen mit Zervixkarzinom gewinnen. Eingeschlossen wurden Frauen mit histologisch gesichertem Zervixkarzinom welche sich im Zeitraum zwischen dem 10.09.2008 und dem 11.09.2012 am Tikur Anbessa Hospital vorstellten. Patientinnen mit Zervixkarzinom wurden aus allen Teilen des Landes an das Tikur Anbessa Hospital überwiesen. Wir gehen daher trotz des krankenhausbasierten Studiendesigns davon aus, einen großen Teil der am Zervixkarzinom erkrankten Frauen in die Studie mit eingeschlossen zu haben. Auf Basis dieser Datenbank sind in der Folge vier Publikationen entstanden, welche die Grundlage dieser Dissertation bieten.

Ein positives Votum der Ethikkommission der Medizinischen Fakultät der Martin-Luther-Universität Halle-Wittenberg sowie der Universität Addis Abeba liegt vor.

Zum Zeitpunkt der Erhebung im Jahr 2012 gab es keine großangelegten epidemiologischen Studien in Äthiopien zum Thema Zervixkarzinom. An dem von uns erhobenen Datensatz wurden folgende Fragestellungen bearbeitet, welche einen Beitrag zur Schließung dieser Forschungslücke leisten sollen:

1) Gibt es einen Zusammenhang zwischen langen Zeiträumen von Symptombeginn bis Diagnosestellung und fortgeschrittenen Tumorstadien des Zervixkarzinoms?
2) Welche Faktoren sind mit langen Zeiträumen zwischen Symptombeginn und Diagnosestellung assoziiert?
3) Gibt es weitere Faktoren, welche mit fortgeschrittenen Tumorstadien zum Diagnosezeitpunkt assoziiert sind?
4) Was ist der Behandlungserfolg der Therapie in Bezug auf das Gesamtüberleben von Frauen mit Zervixkarzinom in Äthiopien?
5) Welche Nebenwirkungen einer Strahlentherapie des Zervixkarzinoms treten auf? Gibt es einen Zusammenhang von Adhärenz zur Strahlentherapie und Gesamtüberleben der Patientinnen?
6) Welchen Einfluss hat HIV auf das Gesamtüberleben von Patientinnen mit Zervixkarzinom? Gibt es weitere Faktoren, welche das Gesamtüberleben beeinflussen?

2. Diskussion

Eine frühzeitige und leitliniengerechte Diagnostik und Therapie von Patientinnen mit Zervixkarzinom zählt neben Interventionen im Bereich der Primärprävention zu den Säulen der Maßnahmen der WHO, um das Zervixkarzinom in den nächsten 100 Jahren zu eliminieren. Vor diesem Hintergrund werden im Folgenden die vorliegenden Studienergebnisse mit vergleichbaren Arbeiten diskutiert, um den Status klinischer Präsentation von Patientinnen mit Zervixkarzinom, der Therapie sowie deren Aussicht auf Erfolg in Äthiopien zu beleuchten. Der Fokus liegt hierbei auf dem klinischen Bild, den Zeiträumen zwischen Symptombeginn und histologischer Diagnose sowie zwischen der Registrierung im Tikur Anbessa Krankenhaus und dem Therapiebeginn.

2.1 Klinisches Bild und Tumorstadium zum Zeitpunkt der Diagnose

Zum Zeitpunkt der Datenerhebung stellten sich nahezu alle Patientinnen mit einem Zervixkarzinom mit einer symptomatischen Tumorerkrankung vor. Mehr als 90 % der Patientinnen litten an vaginalen Blutungen. 73,1 % berichteten über vaginalen Ausfluss und 71,9 % der Frauen klagten über Schmerzen im Unterleib. Obstipation wies auf einen fortgeschrittenen Tumorprozess hin. So befanden sich 64 % der Frauen, welche unter Obstipation litten, in einem FIGO-Stadium IIIb oder höher (21). Da Präkanzerosen und frühe Tumorstadien häufig asymptomatisch verlaufen, ist eine Diagnose in einem bereits symptomatischen Stadium der Erkrankung meist mit fortgeschrittenen Tumorstadien und folglich schlechterer Prognose vergesellschaftet. Ein Großteil der Patientinnen wurde in weit fortgeschrittenen Tumorstadien diagnostiziert. Zum Zeitpunkt der ersten Untersuchung durch einen Onkologen im Tikur Anbessa Hospital befanden sich bereits fast die Hälfte der Patientinnen (46,7 %) im FIGO-Stadium IIb-IIIa, während 34,2 % der Frauen ein FIGO-Stadium von IIIb-IVb aufwiesen. Nur 16,4 % der Frauen qualifizierten sich mit frühem FIGO-Stadium I-IIa für eine operative Therapie (22).

Diese Zahlen sind vergleichbar mit Daten aus der südafrikanischen Stadt Kapstadt, in der von 1984 bis 2000 kein Zervixkarzinom-Screening durchgeführt wurde (23). Als Beispiel für ein Land mit hoher Screening-Aktivität wurden in Deutschland in einem vergleichbaren Zeitraum 66 % der Frauen mit T1-Tumor und 22 % der Frauen mit T2 Tumor diagnostiziert, also häufiger in einem früheren Tumorstadium (24). Das in unserer Studie beobachtete klinische Bild zum Diagnosezeitpunkt spiegelt zunächst die Abwesenheit von Screeningmaßnahmen wider in denen Frauen bereits mit asymptomatischen Präkanzerosen oder früheren Tumorstadien diagnostiziert werden können, und folglich häufig mit kurativem Ansatz therapiert werden.

Um die von der WHO geforderte Screeningrate von 70 % sowie eine Behandlungsrate von 90 % aller Präkanzerosen zu erreichen, müssen Einrichtungen, in denen sowohl Diagnostik als auch die Behandlung von Präkanzerosen stattfinden, rapide ausgebaut werden. Jedoch erhielten nach einer 2003 in Äthiopien durchgeführten Befragung im Rahmen des World Health Surveys der WHO lediglich 0,6 % der Frauen ein Zervixkarzinom-Screening innerhalb der letzten 3 Jahre (25).

Das klinische Bild mit nahezu ausschließlich symptomatischen Patientinnen ist außerdem Ausdruck mangelnden Wissens über die Erkrankung seitens der Patientinnen. So haben Studien aus verschiedenen Teilen Äthiopiens gezeigt, dass in der Bevölkerung wenig über die Entstehung, Vorsorge und Symptomatik des Zervixkarzinoms bekannt ist (26–29). In einer Erhebung aus Uganda wurden entsprechende Symptome wie vaginale Blutungen oder Ausfluss häufig als harmlos, zum Beispiel im Rahmen normaler körperlicher Veränderungen interpretiert (30). Mangelndes Wissen trägt dadurch zu einer Verzögerung der Diagnose durch die Verlängerung des Zeitraums zwischen Symptombeginn und Diagnose bei (31). Dieser Zeitraum wird im Folgenden eingehend betrachtet.

2.2 Zeitraum zwischen Symptombeginn und histologischer Diagnose

Einer der wichtigsten prognostischen Faktoren des Zervixkarzinoms ist das FIGO-Stadium zum Diagnosezeitpunkt. Tumordiagnosen in einem fortgeschrittenen Tumorstadium sind mit einem schlechteren Gesamtüberleben assoziiert (32). Wir zeigten in unserer Studie, dass längere Zeiträume zwischen Symptombeginn und pathologischer Tumordiagnose mit fortgeschrittenen FIGO-Stadien assoziiert waren. Die mediane Dauer zwischen Symptombeginn und pathologischer Diagnose, lag bei 30 Wochen. Patientinnen, welche in frühen FIGO-Stadien I-IIa diagnostiziert wurden, wiesen mit durchschnittlich 24 Wochen die kürzesten Zeiträume zwischen Symptombeginn und pathologischer Diagnose auf, während die Zeiträume von Patientinnen mit weit fortgeschrittenen FIGO-Stadien IV mit 35 Wochen an längsten waren. Insbesondere bei Frauen aus ländlichen Regionen, welche häufig lange Transportwege zu medizinischen Einrichtungen auf sich nehmen müssen, vergingen lange Zeiträume zwischen Symptombeginn und Diagnose (21).

Mögliche Ursachen für lange Zeiträume zwischen Symptombeginn und histologischer Diagnosestellung sind vielfältig (33). Neben dem bereits erwähnten fehlenden Wissen der Patientinnen können Verzögerungen der Diagnose sowohl durch Fehldiagnosen als auch Fehleinschätzungen und folglich Verzögerungen von Überweisung und Diagnostik aufgrund nicht ausreichender Ausbildung des medizinischen Personals entstehen.

So stellten zwei Studien in Äthiopien durch Befragungen medizinischen Fachpersonals ein lückenhaftes Wissen über die Risikofaktoren, die assoziierten Symptome sowie mangelnde Kenntnisse über die Durchführung entsprechender Screeningmaßnahmen heraus (34,35). Angst vor sozialer Stigmatisierung stellt laut Birhanu et al. einen weiteren Faktor dar, welcher das Aufsuchen medizinischer Einrichtungen verzögert und folglich zu längeren Zeiträumen bis zur Diagnose führt (36). Ferner spielen hohe finanzielle Kosten, wie beispielsweise Aufwendungen für Transportwege oder Unterbringung in Addis Abeba eine bedeutsame Rolle (37,38). Wichtig ist daher zu betonen, dass die langen Wartezeiten multifaktoriell bedingt und nicht allein auf die Patientinnen zurückzuführen sind. Sozioökonomische Faktoren und Lücken in den Versorgungsstrukturen des Gesundheitssystems beeinflussen die Wartezeiten ebenfalls. Eine vergleichbare Studie aus Nepal, welche auch die Zeiträume zwischen Symptombeginn und histologischer Diagnose bei Patientinnen mit Zervixkarzinom untersuchte, fand kürzere mediane Zeiträume von 22 Wochen (39). In einer aktuellen prospektiven Studie untersuchten Dereje et al. Ausmaß und Ursachen von langen Wartezeiten zwischen Symptombeginn und Diagnosezeitpunkt bei Patientinnen mit Zervixkarzinom aus dem populationsbezogenen Krebsregister in Addis Abeba. Dieser Zeitraum wurde von den Autor*innen in ein *health seeking interval* (Zeitpunkt zwischen Bemerken der ersten Symptome und der ersten Konsultation einer Gesundheitsversorger*in) sowie in ein *diagnostic interval* (Zeitraum zwischen erster Konsultation einer Gesundheitsversorger*in und histologischer Diagnose) unterteilt. Die Autor*innen fanden kürzere Wartezeiten als in unserer Studie mit einem medianen *health seeking Interval* von 10 Tagen, wobei knapp ein Viertel der Patientinnen später als 90 Tage nach Bemerken des Symptoms eine/n Gesundheitsversorger*in konsultierte. Prädiktoren für lange Intervalle waren ein mangelndes Krankheitsbewusstsein, das Praktizieren religiöser Praktiken zur Bekämpfung der Krankheit sowie das Warten auf weitere Symptome vor dem Aufsuchen einer medizinischen Einrichtung. Das *diagnostic interval* lag im Median bei 97 Tagen. Bei mehr als dreiviertel der Patientinnen lag eine verlängerte Wartezeit von über 30 Tagen vor. Besonders Frauen, welche zuerst Gesundheitseinrichtungen der Primärversorgung (sog. *Health center* und private Praxen) konsultierten, benötigten häufig mehrere Arztbesuche bis zur Diagnose und hatten dadurch lange Wartezeiten (40). Ursache für die kürzeren Wartezeiten bei Dereje et al. sind der größere Anteil einer urbanen Bevölkerungsschicht mit wohnortnäherer Versorgung und könnten durch ein steigendes Bewusstsein für das Zervixkarzinom, sowohl von den betroffenen Frauen als auch den Angestellten in Gesundheitsberufen, begründet sein.

2.3 Wartezeit auf die Therapie

Neben langen Zeiträumen zwischen Symptombeginn und pathologischer Diagnose verging viel wertvolle Zeit zwischen Diagnose und Therapiebeginn. Wir untersuchten die Wartezeit bei 1059 Patientinnen mit invasivem Zervixkarzinom welche eine Therapie – Operation oder Strahlentherapie – im Tikur Anbessa Hospital erhielten. Fast ein Drittel der Patientinnen, welche sich im Tikur Anbessa Hospital aufgrund einer Zervixkarzinomdiagnose registrierten, erschienen nicht zu den geplanten Voruntersuchungen und erhielten folglich keine Therapie. Es ist davon auszugehen, dass ein Großteil der Frauen in diesem Zeitraum verstorben ist.

Die Wartezeit zwischen Registrierung im Tikur Anbessa Hospital und OP-Termin der 84 Patientinnen mit primär operativer Therapie betrug im Median 2,1 Monate (22). Da zwischen Diagnose und Registrierung im Krankenhaus zusätzliche Zeit einberechnet werden muss, ist die Wartezeit zwischen Diagnose und Operation noch länger. Eine aktuelle Studie mit einer Kohorte US-amerikanischer Patientinnen fand kürzere mediane Wartezeiten zwischen Diagnose und operativer Therapie von 4 Wochen. Längere Wartezeiten waren in der Studie nicht mit einer höheren Mortalität, jedoch mit einem häufigeren Tumorbefall der Parametrien assoziiert (41). Die Wartezeit auf eine operative Therapie eines Zervixkarzinoms sollte daher weiter reduziert werden, zum Beispiel durch gezielte Schulungen entsprechender Operationstechniken wie der Wertheim-Meigs-Operation von Chirurg*innen und Gynäkolog*innen aus Krankenhäusern jenseits des Tikur Anbessa Hospitals und Addis Abeba.

Bei Patientinnen mit weiter fortgeschrittenen Tumorstadien, welche mit primärer Strahlentherapie behandelt wurden, vergingen zwischen erster Registrierung im Tikur Anbessa Hospital und Beginn der Bestrahlung im Median ganze 3,8 Monate. Leider mussten wir beobachten, dass es in diesem Zeitraum bei einem großen Anteil der Patientinnen zu einem Anstieg des FIGO-Stadiums kam („upstaging“). So vergrößerte sich der Anteil der Patientinnen mit FIGO Stadium IIIb oder höher von 44,2 % zum Zeitpunkt des ersten Termins beim Onkologen auf 68,3 % zu Beginn der Strahlentherapie (22). Längere Wartezeiten als drei Monate zwischen Diagnose und Therapiebeginn waren laut Chao-Ping Chen et al. mit einem geringeren Gesamtüberleben assoziiert. Sie untersuchten in einer 2019 publizierten Studie den Einfluss der Wartezeit bei Patientinnen mit Zervixkarzinom in Taiwan (42). In Äthiopien beträgt die Zeit bis zum Beginn der Strahlentherapie deutlich länger. So zeigten Feuchtner et al. in ihrer Untersuchung zur Wartezeit auf eine Strahlentherapie der am häufigsten bestrahlten Tumoren (Brust, Zervix, Kopf & Hals, Rektum) in den Jahren 2012-2014 am Tikur Anbessa Hospital eine mittlere Wartezeit von nahezu 7 Monaten zwischen Therapieplanung und Therapiebeginn.

Dies war auf steigende Patient*innenzahlen bei begrenzter Anzahl an Therapieplätzen zurückzuführen (43).

Die Finanzierung weiterer Bestrahlungsgeräte, deren Instandhaltung sowie die Beschäftigung von geschultem Personal sind demnach unerlässlich, um die Wartezeit auf eine Strahlentherapie zu verkürzen und eine Verschlechterung der Prognose betroffener Frauen zu verhindern. In einer 2013 publizierten Studie beschrieben Abdel Wahab et al. Äthiopien als Land mit der zweitgrößten Diskrepanz zwischen dem Bedarf und dem Vorhandensein von Bestrahlungsgeräten (44). Zu dieser Zeit bestand laut den Autor*innen in Äthiopien ein Bedarf von 72 Geräten bei lediglich einem vorhandenen Gerät. In 28 afrikanischen Ländern existierte im Jahr 2017 kein einziges Bestrahlungsgerät (45).

2.4 HIV und Zervixkarzinom

Neben dem Zervixkarzinom stellen HIV und AIDS Subsahara-Afrika vor weitere massive Herausforderungen. Hier leben knapp 70 % der weltweit mit HIV Infizierten Menschen (46). Im Gegensatz zu Ländern des globalen Nordens erkranken in Subsahara-Afrika zunehmend Frauen an HIV. So treten hier vier von fünf Neuansteckungen bei Jugendlichen im Alter von 15-19 bei Mädchen auf (47).

Die Interaktionen von HIV und HPV sind vielfältig. Zunächst infizieren sich HIV-positive Frauen doppelt so häufig mit einem oder mehreren HPV-Stämmen (48,49). Darüber hinaus begünstigt eine HIV-Infektion die Persistenz der HPV-Infektionen in der Mukosa der Zervix und folglich die Entwicklung von Präkanzerosen und invasiven Zervixkarzinomen (50–53). Dieser Effekt ist besonders ausgeprägt bei immunsupprimierten Patientinnen mit niedriger CD4-Zellzahl sowie Patientinnen die keine antiretrovirale Therapie (ART) erhalten (54–56). Daraus folgt ein sechsfach erhöhtes Risiko HIV-positiver Frauen, ein Zervixkarzinom zu entwickeln (57,58). Umgekehrt haben Frauen mit HPV-Infektion laut einer 2012 erschienenen Metaanalyse ein zweifach erhöhtes Risiko einer Infektion mit HIV (59). Die biologischen Mechanismen hinter dem Zusammenhang von HIV und HPV sind noch nicht vollständig ergründet (60). Aufgrund der erhöhten Erkrankungswahrscheinlichkeit HIV-positiver Frauen erklärte das Center of Disease Control im Jahr 1993 das invasive Zervixkarzinom zur AIDS-definierenden Erkrankung (61).

In unserer Kohorte hatten 8,6 % der Frauen eine bekannte HIV-Infektion, 23,2 % waren bekannt negativ (21). Diese Anzahl der bekannt HIV-positiven liegt deutlich über dem nationalen Durchschnitt von 1,2 % bei 15-49 jährigen Frauen. Erst im September 2011 wurde ein umfassendes HIV-Screening aller Patientinnen mit Zervixkarzinom im Tikur Anbessa Hospital eingeführt, weshalb der HIV-Status bei 1081 Frauen (68,2 %) unbekannt war.

Zuvor wurden nur Hochrisikopatientinnen auf HIV getestet, beispielsweise solche mit HIV-positivem Partner. Mit 39 Jahren war die Gruppe HIV-positiver Patientinnen zum Diagnosezeitpunkt in unserer Studie im Mittel 10 Jahre jünger als die Gruppe HIV-negativer Frauen und Frauen mit unbekanntem HIV-Status. Diese Beobachtung des jüngeren Erkrankungsalters bei HIV positiven Frauen deckt sich mit mehrfach publizierten Studienergebnissen (62–64). Des Weiteren konnten wir einen positiven HIV-Status als Prädiktor eines fortgeschrittenen FIGO-Stadiums identifizieren. So hatten HIV-positive Frauen unserer Kohorte ein 1,5-fach erhöhtes Risiko in einer höheren FIGO-Gruppe diagnostiziert zu werden im Vergleich zu HIV-negativen Frauen und Frauen mit unbekanntem HIV-Status (21). Erfreulicherweise war ein positiver HIV-Status keine unabhängiger Prädiktor für geringere Überlebensraten (65). Zu ähnlichen Ergebnissen kam eine prospektive Kohortenstudie aus Botswana aus dem Jahr 2021, welche keine schlechtere Fünf-Jahres-Überlebensrate nach erfolgter Radiochemotherapie bei Patientinnen mit Zervixkarzinom und adäquat behandelter HIV-Infektion im Vergleich mit HIV-negativen Patientinnen fand (66).

Diese Ergebnisse stehen im Kontrast mit vergleichbaren Studien aus Südafrika, Botswana und Brasilien, welche in früheren Zeiträumen vor der breiten Verfügbarkeit von ART und bei Patientinnen mit niedrigeren CD4-Zellzahlen durchgeführt wurden und schlechtere Überlebensraten von HIV-positiven Patientinnen mit Zervixkarzinom zeigten (64,67,68).
Dies unterstreicht den wichtigen Stellenwert der ART für HIV-positive Patientinnen mit Zervixkarzinom. In diversen Studien konnte zudem gezeigt werden, dass Patientinnen mit adäquat behandelter HIV-Infektion keine höhere Unverträglichkeitsraten auf eine Radiochemotherapie aufwiesen, verglichen mit HIV-negativen Patientinnen (69,70). Eine leitliniengerechte Therapie des Zervixkarzinom sollte daher unabhängig des HIV-Status der Patientin erfolgen.

Die in unserer Studie betrachteten HIV-positiven Frauen stellen eine Hochrisikogruppe für die Entwicklung eines früh entstehenden und womöglich schneller progredienten invasiven Zervixkarzinoms. Es ist demnach sinnvoll, Präventionsmaßnahmen wie Impfung, Screening und Aufklärungsarbeit für diese Gruppe von Patientinnen in besonderem Maße zu verstärken. Die zunehmende Verbreitung von HIV-Medikamenten und die damit einhergehende Einbindung der Frauen ins Gesundheitssystem sowie bestehende Einrichtungen zur HIV-Prävention könnten als Schnittstelle für HIV-Therapie und Zervixkarzinom-Prävention fungieren. So sollte beispielsweise jeder Frau bei Diagnosestellung einer HIV-Infektion ein HPV-Screening mit regelmäßigen Folgeuntersuchungen angeboten werden.

2.5 Therapie

Von den insgesamt 1655 Patientinnen erhielten 1059 eine Therapie. 158 Patientinnen erhielten aufgrund früher FIGO-Stadien eine operative Therapie, wobei bei 111 Patientinnen eine adjuvante Strahlentherapie folgte, während 47 Patientinnen ausschließlich operiert wurden. 1012 der Patientinnen erhielten eine transkutane Strahlentherapie mit einer Cobalt-60 Einheit. 27,5 % der Frauen, welche bestrahlt wurden, erhielten eine sogenannte radikale Strahlendosis von kumulativ 60-72 Gy. 45,3 % der Patientinnen erhielten eine reduzierte Strahlendosis von kumulativ 44-50 Gy, während 27,1 % der Patientinnen eine rein palliative Strahlentherapie in sogenannten *single shots* mit einer kumulativen Strahlendosis von 32 Gy erhielten. Trotz eindeutig belegter verbesserter Prognose erhielten nur 17,1 % aller Patientinnen eine simultane oder adjuvante Chemotherapie (71,72). Wir gehen davon aus, dass für den niedrigen Anteil von Patientinnen mit Chemotherapie neben gesundheitlichen Faktoren wie erhöhten Nierenretentionsparametern oder einem niedrigen Karnofsky-Index vor allem finanzielle und ressourcenbezogene Faktoren verantwortlich sind. Denn Chemotherapeutika sind teuer und sowohl die Anzahl der Arzneimittel als auch die Bettenplätze im Krankenhaus, die zur Verabreichung benötigt werden, sind limitiert (43,73).

Neben einer perkutanen Strahlentherapie wird die Kombination mit einer intrakavitären Brachytherapie bei Patientinnen mit FIGO-Stadium IIb-IVa aufgrund verbesserter Therapieerfolge dringend empfohlen. Han et al. zeigten einen positiven Effekt intrakavitärer Brachytherapie auf das Gesamtüberleben 2013 in einer Studie mit 7359 Patientinnen mit Zervixkarzinom (74). Kim et al. bestätigten diese Erkenntnisse 2021 in einer großangelegten Studie mit 12,721 Patientinnen (75). Durch Brachytherapie wird eine erhöhte Gesamtdosis von 80-95 Gy im Zentrum des Tumors angestrebt (76). Im Jahr 2010 war die intrakavitäre Brachytherapie in nur 20 von 53 afrikanischen Staaten verfügbar – Äthiopien war nicht darunter (77).

2.6 Gesamtüberleben von Patientinnen mit Zervixkarzinom nach Therapie

Innerhalb der Kohorte der 1059 Patientinnen, welche eine Therapie erhalten hatten, registrierten wir 212 Todesfälle. 378 Patientinnen konnten nicht telefonisch erreicht werden oder erschienen nicht zu geplanten Nachsorgeuntersuchungen und waren somit zensiert. Aus diesem Grund errechneten wir sowohl ein Gesamtüberleben mit den vorhandenen Daten als auch ein Worst-Case-Szenario in welchem wir davon ausgingen, dass Patientinnen, welche *zensiert* wurden, einen Tag nach dem letzten registrierten Kontakt verstarben. Die geschätzten Ein- und Zwei-Jahres-Überlebensraten der Kohorte betrugen 90,4 % beziehungsweise 73,6 %.

Im Worst-Case-Szenario reduzierte sich das Zwei-Jahres-Gesamtüberleben von 73,6 % auf 45,4 %. Die mediane Überlebenszeit betrug 40,6 Monate und im Worst-Case-Szenario 21,5 Monate. Die Zwei-Jahres-Überlebensrate war am besten für Patientinnen mit niedrigem FIGO-Stadium I-IIa und verschlechterte sich jeweils mit fortschreitendem FIGO-Stadium. Am schlechtesten war sie für Patientinnen im höchsten FIGO-Stadium IVb (22). Es ist davon auszugehen, dass in der Kohorte dieser Studie insbesondere Patientinnen mit weit fortgeschrittenem Tumorleiden unterrepräsentiert sind, da diese mit größerer Wahrscheinlichkeit bereits vor Therapiebeginn verstorben sind. Ferner ist anzunehmen, dass insbesondere Patientinnen aus ländlichen Regionen in reduziertem Allgemeinzustand aufgrund eines weit fortgeschrittenen Tumorstadiums den – teils beschwerlichen und teuren – Weg in die Hauptstadt Addis Abeba auf der Suche nach Therapie nicht mehr antreten können. Aufgrund unserer Krankenhaus-Kohorte gehen wir daher davon aus, dass das errechnete Gesamtüberleben gegenüber einer populationsbezogenen Kohorte vorteilhafter ausfällt. Daten aus einem populationsbezogenen Krebsregister in der ugandischen Hauptstadt Kampala zeigen eine Fünf-Jahres-Überlebensrate von 19 % in den Jahren 1993-1997 (78). In Harare, Zimbabwe, lag die Drei-Jahres-Überlebensrate bei 44,2 %, wobei hier nur die Hälfte der Patientinnen in der Kohorte bestrahlt wurden (79). Eine weitere Studie ergab eine Fünf-Jahres-Überlebensrate von 22 % in Gambia und 13 % in Uganda (80). Die Zwei-Jahres-Überlebensrate von fast 74 % in unserer Studie lag somit über jenen, welche in Zimbabwe, Gambia und Uganda erhoben wurden. Einerseits könnte dies zum Teil dem vermuteten Fehlen einiger Patientinnen mit weit fortgeschrittenen Tumorstadien zugeschrieben werden. Andererseits kann dies auch als Hinweis für einen positiven Effekt der in Addis Abeba praktizierten Strahlentherapie gedeutet werden. Neben dem FIGO-Stadium war ein hohes Patientinnenalter über 60 Jahre sowie das Vorliegen einer Anämie ein unabhängiger Prädiktor für ein schlechteres Gesamtüberleben. Diese Beobachtungen sind kongruent mit den Erkenntnissen diverser, publizierter Studien (66,81–83).

2.7 Effekt und Nebenwirkungen der Strahlentherapie sowie Therapieadhärenz der Patientinnen

Patientinnen mit Zervixkarzinom, welche die Strahlentherapie frühzeitig abbrachen, hatten in unserer Studie mit 788 Patientinnen derselben Kohorte ein reduziertes Gesamtüberleben (84). Fast die Hälfte der Patientinnen, die eine radikale Strahlentherapie erhalten sollten, erhielten nicht die geplante kumulative Strahlendosis. Bei Patientinnen mit nicht radikaler Strahlentherapie fiel der Anteil an Therapieabbrüchen mit 17 % geringer aus.

Die Ursache für einen großen Anteil aller Therapieabbrüche waren Nebenwirkungen durch die Strahlentherapie. Wir dokumentierten eine Strahlendermatitis in 9 % sowie Diarrhö in 12 % aller Fälle. Noch häufiger wurden Spätfolgen der Strahlentherapie erfasst, was sich im Rahmen von Nachsorgeuntersuchungen sowie der telefonischen Nachsorge von 440 Frauen herausstellte.
43 % der Frauen litten unter Dysurie aufgrund einer nichtinfektiösen Zystitis und bei 41 % der Frauen wurde eine suprapubische Fibrose festgestellt. Weitere erfasste, späte Nebenwirkungen waren Harninkontinenz (22 %), vesicovaginale Fistelbildung (17 %) sowie vaginale Enge (13 %).

Diese Nebenwirkungen führen zu deutlichen Einbußen der Lebensqualität der Frauen. Die Beobachtungen unterstreichen einerseits die Notwendigkeit einer breiten Implementierung der intrakavitären Brachytherapie und andererseits den Bedarf an supportiven Maßnahmen wie Schmerztherapie und psychosoziale Betreuung zur Milderung der Nebenwirkungen und Verbesserung der Lebensqualität.

Auch finanzielle oder logistische Faktoren wurden als Grund für als Grund für frühzeitige Therapieabbrüche genannt. Um die Therapieadhärenz zu verbessern, sind demnach Maßnahmen zur finanziellen und organisatorischen Unterstützung der Patientinnen notwendig.

2.8. Stärken und Limitationen

Stärken der vorliegenden Arbeit sind die große Zahl der bis zu 1655 eingeschlossenen Patientinnen mit nachgewiesenem invasivem Zervixkarzinom. Nach unserem Wissen ist dies die größte retrospektive Studie über die klinische Präsentation und die Behandlung von Patientinnen mit Zervixkarzinom in Subsahara-Afrika. Auch die Inklusion von Informationen über 516 Patientinnen, welche keine Therapie erhalten hatten, gehört zu den Stärken der Studie. Eine Limitation liegt insbesondere in der retrospektiven Datenerhebung. So wurde ein Großteil der Daten aus handschriftlichen Patientinnenakten akquiriert, welche nicht immer vollständig waren. Einige Informationen wie der Zeitpunkt des Symptombeginns beruhten auf Selbsteinschätzungen der Patientinnen, welche – insbesondere bei langen Zeiträumen – von einer Erinnerungsverzerrung betroffen sein können. Jedoch wurden diese Informationen ausschließlich von drei praktizierenden Onkologen erhoben, sodass von ähnlichen Fragetechniken auszugehen ist. Weiter müssen wir von einer gewissen Selektionsverzerrung ausgehen, da nur im Tikur Anbessa Hospital vorstellige Frauen in die Studien eingeschlossen wurden. Insbesondere Frauen aus ländlichen Regionen, welche den Weg in die Hauptstadt aufgrund weit fortgeschrittener Tumorstadien und folglich reduziertem Allgemeinzustand nicht mehr auf sich nehmen konnten, könnten daher in der Studie fehlen. Dies würde zu einer positiven Verzerrung des Outcomes führen. Möglich ist auch eine Unterrepräsentation von Patientinnen in sehr frühen Tumorstadien, welche eine sogenannte einfache Hysterektomie ohne anschließende Radiochemotherapie in einem anderen Krankenhaus erhalten hatten und daher niemals im Tikur Anbessa Hospital vorstellig wurden. Aufgrund niedriger landesweiter Screeningraten ist jedoch davon auszugehen, dass dieser Anteil gering ist.

2.9. Fazit

Noch immer stellt das Zervixkarzinom für Frauen eine reale Bedrohung von Gesundheit und Leben dar. Dies ist vor allem in LMICs der Fall, in denen die überwältigende Mehrheit der Erkrankungs- und Todesfälle vorkommen. Trotz allem besteht auch in Äthiopien, wo das Zervixkarzinom zu den häufigsten Tumoren zählt, ein Mangel an epidemiologischen Studien. Mit einer großangelegten Datenerhebung im Tikur Anbessa Hospital in der äthiopischen Hauptstadt Addis Abeba sollte ein Beitrag zur Schließung dieser Forschungslücke geleistet werden. Die Erkenntnisse aus den vier besprochenen Studien bieten ein umfassendes Bild über die klinische Präsentation, die Hürden auf dem Weg zur Therapie und das Überleben von über 1500 Frauen welche im Zeitraum September 2008 – September 2012 mit invasivem Zervixkarzinom im Tikur Anbessa Hospital registriert wurden. Wir sahen viele HIV-positive Frauen, welche im Mittel über 10 Jahre früher als Frauen mit negativem oder unbekannten HIV-Status erkrankten. Auch wurden diese Frauen mit weiter fortgeschrittenen FIGO-Stadien diagnostiziert. Da diese Patientinnengruppe besonders vulnerabel für die Entwicklung eines invasiven Zervixkarzinoms in jungem Alter und eine Diagnose in fortgeschrittenem Stadium ist, müssen Aufklärung und Screening in besonderem Maße auf sie angepasst werden. Bestehende medizinische Infrastruktur zur HIV-Therapie könnte hierfür genutzt werden. Neben den Maßnahmen der Primärprävention zur Vermeidung der Erkrankung ist für bereits erkrankte Frauen eine frühzeitige Diagnose sowie ein rascher Therapiebeginn von essenzieller Bedeutung für den Behandlungserfolg. Das Angebot sollte bei bereits medizinisch angebundenen Patientinnen mit HIV sensibel integriert werden. Bei der Auswertung der Daten stellten wir zwischen Symptombeginn und Diagnosestellung jedoch lange Zeiträume fest, welche mit weiter fortgeschrittenen Tumorstadien assoziiert waren. Insbesondere Frauen aus ländlichen Regionen wiesen längere Wartezeiten auf. Um die Diagnosestellung zu beschleunigen, muss demnach dringend medizinische Infrastruktur auch abseits urbaner Regionen ausgebaut werden. Außerdem sollte das Bewusstsein für die Erkrankung und deren Symptome durch gezielte Kampagnen und Schulungen gestärkt werden. Weiterhin kam es in vielen Fällen aufgrund langer Wartezeiten bis zum Therapiebeginn zu einem weiteren Fortschreiten der Tumorausbreitung und einem Anstieg des Tumorstadiums. Auch dies unterstreicht die Notwendigkeit des Ausbaus personeller und apparativer Ressourcen, um diese Wartezeiten zu verkürzen. Wir stellten im Vergleich mit HICs deutlich schlechtere Gesamtüberlebensraten fest. Es ist davon auszugehen, dass dies zunächst an den weit fortgeschrittenen Tumorstadien der meisten Frauen zum Diagnosezeitpunkt lag.

Zudem unterscheidet sich der Therapieumfang in Äthiopien von HICs durch die Abwesenheit intrakavitärer Brachytherapie und das häufige Fehlen von Chemotherapie. Dennoch war das beobachtete Gesamtüberleben günstiger als in anderen Ländern Subsahara-Afrikas, in denen keine perkutane Strahlentherapie durchgeführt wurde. Daher ist das Vorhandensein dieser Therapieform ein wichtiger Baustein zur Verringerung von Mortalität und Morbidität in Äthiopien. Auch das Auftreten von Nebenwirkungen der Strahlentherapie, welche zu häufigen Therapieabbrüchen geführt haben, unterstützt das Erfordernis einer flächendeckenden Verfügbarkeit intrakavitärer Brachytherapie zur Limitierung strahlungsassoziierter Nebenwirkungen. Die Patientinnen mit unvollständig durchgeführter Strahlentherapie hatten ein reduziertes Gesamtüberleben. Abschließend lassen sich folgende wichtige Ansätze herausstellen, um das Zervixkarzinom als zentrales Gesundheitsproblem zu bekämpfen und das Leid zahlreicher äthiopischer Frauen zu reduzieren: Die Reduktion der Zeit zwischen Symptombeginn und Diagnose und der Wartezeit bis zum Therapiebeginn, die Fokussierung auf HIV-positive Frauen als Hochrisikogruppe sowie die Verbesserung der Therapie durch flächendeckend verfügbare intrakavitäre Brachytherapie und Chemotherapie. Nur so kann ein Beitrag zur Erfüllung des durch die WHO ausgerufenen Ziels, das Zervixkarzinom in den nächsten 100 Jahren zu eliminieren, geleistet werden.

3. Literaturverzeichnis

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA A Cancer J Clin*. 2021;71(3):209–49.

2. Small W, Bacon MA, Bajaj A, Chuang LT, Fisher BJ, Harkenrider MM, et al. Cervical cancer: A global health crisis. *Cancer*. 2017;123(13):2404–12.

3. Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. *Lancet*. 2019;393(10167):169-182.

4. Anorlu RI. Cervical cancer: the sub-Saharan African perspective. *Reprod Health Matters*. 2008;16(32):41-49.

5. Denny L. Control of cancer of the cervix in low- and middle-income countries. *Ann Surg Oncol*. 2015;22(3):728-733.

6. Momberg M, Botha MH, Van der Merwe FH, Moodley J. Women's experiences with cervical cancer screening in a colposcopy referral clinic in Cape Town, South Africa: a qualitative analysis. *BMJ Open*. 2017;7(2):e013914.

7. Mwaka AD, Okello ES, Wabinga H, Walter FM. Symptomatic presentation with cervical cancer in Uganda: a qualitative study assessing the pathways to diagnosis in a low-income country. *BMC Womens Health*. 2015;15:15.

8. Dolea C. Increasing access to health workers in remote and rural areas through improved retention: global policy recommendations. Geneva, Switzerland: World Health Organization; 2010. 72 S.

9. Central Statistical Agency (CSA) [Ethiopia] and ICF. 2016. *Ethiopia Demographic and Health Survey 2016: Key Indicators Report*. Addis Ababa, Ethiopia, and Rockville, Maryland, USA. CSA and ICF. [zitiert 1. Mai 2020]. Verfügbar unter: https://dhsprogram.com/publications/publication-fr328-dhs-final-reports.cfm

10. Wild CP, Weiderpass E, Stewart BW, editors. *World Cancer Report: Cancer Research for Cancer Prevention*. Lyon, France: International Agency for Research on Cancer; 2020 [zitiert 1. Mai 2020]. Verfügbar unter: http://publications.iarc.fr/586.

11. Zhang S, Xu H, Zhang L, Qiao Y. Cervical cancer: Epidemiology, risk factors and screening. *Chin J Cancer Res*. 2020;32(6):720-728.

12. Hiddemann W, Bartram CR. *Die Onkologie: Teil 1: Epidemiologie - Pathogenese - Grundprinzipien der Therapie; Teil 2: Solide Tumoren - Lymphome - Leukämien*. Berlin: Springer; 2009.

13. Fesenfeld M, Hutubessy R, Jit M. Cost-effectiveness of human papillomavirus vaccination in low and middle income countries: a systematic review. Vaccine. 2013;31(37):3786-3804.

14. Jit M, Brisson M. Potential lives saved in 73 countries by adopting multi-cohort vaccination of 9-14-year-old girls against human papillomavirus. *Int J Cancer.* 2018;143(2):317-323.

15. Campos NG, Sharma M, Clark A, et al. The health and economic impact of scaling cervical cancer prevention in 50 low- and lower-middle-income countries. *Int J Gynaecol Obstet*. 2017;138 Suppl 1:47-56. doi:10.1002/ijgo.12184

16. Campos NG, Tsu V, Jeronimo J, Mvundura M, Lee K, Kim JJ. When and how often to screen for cervical cancer in three low- and middle-income countries: A cost-effectiveness analysis. *Papillomavirus Res*. 2015;1:38-58.

17. Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. *Lancet Glob Health*. 2014;2(7):e406-e414.

18. Draft: Global strategy towards eliminating cervical cancer as a public health problem. WHO; 2020 [zitiert 1. Mai 2020]. Verfügbar unter: https://www.who.int/docs/default-source/cervical-cancer/cervical-cancer-elimination-strategy-updated-11-may-2020.pdf

19. B Brisson M, Kim JJ, Canfell K, Drolet M, Gingras G, Burger EA, et al. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. *Lancet*. 2020;395(10224):575-590.

20. Canfell K, Kim JJ, Brisson M, Keane A, Simms KT, Caruana M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. *Lancet*. 2020;395(10224):591-603.

21. Begoihn M, Mathewos A, Aynalem A, Wondemagegnehu T, Moelle U, Gizaw M, et al. Cervical cancer in Ethiopia – predictors of advanced stage and prolonged time to diagnosis. *Infect Agents Cancer*.2019;14(1):36.

22. Kantelhardt EJ, Moelle U, Begoihn M, Addissie A, Trocchi P, Yonas B, et al. Cervical Cancer in Ethiopia: Survival of 1,059 Patients Who Received Oncologic Therapy. *Oncologist*.2014;19(7):727–34.

23. Denny L, Anorlu R. Cervical cancer in Africa. *Cancer Epidemiol Biomarkers Prev*. 2012;21(9):1434-1438.

24. Robert Koch Institut (Hrsg. und die Gesellschaft der Epidemiologischen Krebsregister in Deutschland e.V. (Hrsg.). Krebs in Deutschland 2007/2008: 8. Ausgabe. Berlin, Germany: Agentur Consalis-Media, 2012.

25. Bruni et al. Human Papillomavirus and Related Diseases in the World. Summary Report. [zitiert 1. Mai 2020]. Verfügbar unter: https://www.hpvcentre.net/statistics/reports/XWX.pdf

26. Saleem A, Bekele A, Fitzpatrick MB, Mahmoud EA, Lin AW, Velasco HE, et al. Knowledge and awareness of cervical cancer in Southwestern Ethiopia is lacking: A descriptive analysis. *PLoS One*. 2019;14(11):e0215117.

27. Shiferaw S, Addissie A, Gizaw M, Hirpa S, Ayele W, Getachew S, et al. Knowledge about cervical cancer and barriers toward cervical cancer screening among HIV-positive women attending public health centers in Addis Ababa city, Ethiopia. *Cancer Med*. 2018;7(3):903-912.

28. Getahun F, Mazengia F, Abuhay M, Birhanu Z. Comprehensive knowledge about cervical cancer is low among women in Northwest Ethiopia. *BMC Cancer*. 2013;13:2.

29. Derbie A, Mekonnen D, Misgan E, Alemu YM, Woldeamanuel Y, Abebe T. Low level of knowledge about cervical cancer among Ethiopian women: a systematic review and meta-analysis. *Infect Agent Cancer*. 2021;16(1):11.

30. Mwaka AD, Orach CG, Were EM, Lyratzopoulos G, Wabinga H, Roland M. Awareness of cervical cancer risk factors and symptoms: cross-sectional community survey in post-conflict northern Uganda. *Health Expect*. 2016;19(4):854-867.

31. Simon AE, Waller J, Robb K, Wardle J. Patient delay in presentation of possible cancer symptoms: the contribution of knowledge and attitudes in a population sample from the United kingdom. *Cancer Epidemiol Biomarkers Prev*. 2010;19(9):2272-2277.

32. Waggoner SE. Cervical cancer. *Lancet*. 2003;361(9376):2217-2225.

33. Randall TC, Ghebre R. Challenges in Prevention and Care Delivery for Women with Cervical Cancer in Sub-Saharan Africa. *Front Oncol*. 2016;6:160.

34. Kress CM, Sharling L, Owen-Smith AA, Desalegn D, Blumberg HM, Goedken J. Knowledge, attitudes, and practices regarding cervical cancer and screening among Ethiopian health care workers. *Int J Womens Health*. 2015;7:765-772.

35. Wondimu YT. Cervical Cancer: Assessment of Diagnosis and Treatment. Facilities in Public Health Institutions in Addis Ababa, Ethiopia. *Ethiop Med J.* 2015;53(2):65-74.

36. Birhanu Z, Abdissa A, Belachew T, Deribew A, Segni H, Tsu V, et al. Health seeking behavior for cervical cancer in Ethiopia: a qualitative study. *Int J Equity Health*. 2012;11:83.

37. Hailu A, Mariam DH. Patient side cost and its predictors for cervical cancer in Ethiopia: a cross sectional hospital based study. *BMC Cancer*. 2013;13:69.

38. Hagos A, Yitayal M, Kebede A, Debie A. Economic Burden and Predictors of Cost Variability Among Adult Cancer Patients at Comprehensive Specialized Hospitals in West Amhara, Northwest Ethiopia, 2019. *Cancer Manag Res*. 2020;12:11793-11802.

39. Gyenwali D, Khanal G, Paudel R, Amatya A, Pariyar J, Onta SR. Estimates of delays in diagnosis of cervical cancer in Nepal. *BMC Womens Health*. 2014;14(1):29.

40. Dereje N, Addissie A, Worku A, Assefa M, Abraha A, Tigeneh W, et al. Extent and Predictors of Delays in Diagnosis of Cervical Cancer in Addis Ababa, Ethiopia: A Population-Based Prospective Study. *JCO Glob Oncol*. 2020;6:277-284.

41. Matsuo K, Huang Y, Matsuzaki S, Klar M, Wright JD. Effect of delay in surgical therapy for early-stage cervical cancer: An implication in the coronavirus pandemic. *Eur J Cancer*. 2020;139:173-176.

42. Chen CP, Kung PT, Wang YH, Tsai WC. Effect of time interval from diagnosis to treatment for cervical cancer on survival: A nationwide cohort study. *PLoS One*. 2019;14(9):e0221946.

43. Feuchtner J, Mathewos A, Solomon A, Timotewos G, Aynalem A, Wondemagegnehu T, et al. Addis Ababa population-based pattern of cancer therapy, Ethiopia. *PLoS One*. 2019;14(9):e0219519.

44. Abdel-Wahab M, Bourque JM, Pynda Y, Iżewska J, Van der Merwe D, Zubizarreta E, et al. Status of radiotherapy resources in Africa: an International Atomic Energy Agency analysis. *Lancet Oncol*. 2013;14(4):e168-e175.

45. Abdel-Wahab M, Zubizarreta E, Polo A, Meghzifene A. Improving Quality and Access to Radiation Therapy-An IAEA Perspective. *Semin Radiat Oncol*. 2017;27(2):109-117.

46. Kharsany AB, Karim QA. HIV Infection and AIDS in Sub-Saharan Africa: Current Status, Challenges and Opportunities. *Open AIDS J*. 2016;10:34-48.

47. UNAIDS. Global HIV & AIDS statistics — 2019 fact sheet. [zitiert 30. Mai 2020]. Verfügbar unter: httpswww.unaids.orgsitesdefaultfilesmedia_assetUNAIDS_FactSheet_en.pdf.html

48. Chaturvedi AK, Myers L, Hammons AF, Clark RA, Dunlap K, Kissinger PJ, et al. Prevalence and clustering patterns of human papillomavirus genotypes in multiple infections. *Cancer Epidemiol.* 2005;14(10):2439-2445.

49. McDonald AC, Tergas AI, Kuhn L, Denny L, Wright TC. Distribution of Human Papillomavirus Genotypes among HIV-Positive and HIV-Negative Women in Cape Town, South Africa. Front Oncol. 14. März 2014 [zitiert 30. Mai 2020]. Verfügbar unter: http://journal.frontiersin.org/article/10.3389/fonc.2014.00048/abstract

50. de Sanjosé S, Palefsky J. Cervical and anal HPV infections in HIV positive women and men. *Virus Res*. 2002;89(2):201-211.

51. Feola TD, Albert MB, Shahabi K, Endy T. Prevalence of HPV in HIV-infected women in the Designated AIDS Center at Upstate Medical University and the potential benefit of vaccination regardless of age. *J Assoc Nurses AIDS Care*. 2013;24(2):176-179.

52. Denny L, Boa R, Williamson AL, Allan B, Hardie D, Stan R, et al. Human papillomavirus infection and cervical disease in human immunodeficiency virus-1-infected women. *Obstet Gynecol*. 2008;111(6):1380-1387.

53. Liu G, Sharma M, Tan N, Barnabas RV. HIV-positive women have higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer. *AIDS*. 2018;32(6):795-808.

54. De Vuyst H, Lillo F, Broutet N, Smith JS. HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. *Eur J Cancer Prev*. 2008;17(6):545-554.

55. Denslow SA, Rositch AF, Firnhaber C, Ting J, Smith JS. Incidence and progression of cervical lesions in women with HIV: a systematic global review. *Int J STD AIDS*. 2014;25(3):163-177.

56. Kelly H, Weiss HA, Benavente Y, de Sanjose S, Mayaud P; ART and HPV Review Group. Association of antiretroviral therapy with high-risk human papillomavirus, cervical intraepithelial neoplasia, and invasive cervical cancer in women living with HIV: a systematic review and meta-analysis. *Lancet HIV*. 2018;5(1):e45-e58.

57. Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

58. Stelzle D, Tanaka LF, Lee KK, Ibrahim Khalil A, Baussano I , Shah AS, McAllister DA. Estimates of the global burden of cervical cancer associated with HIV [published correction appears in Lancet Glob Health. 2021 Feb;9(2):e119]. *Lancet Glob Health*. 2021;9(2):e161-e169.

59. UNAIDS 2016: HPV, HIV and cervical cancer: leveraging synergies to save women's lives. [zitiert 1. Mai 2020]. Verfügbar unter: https://www.unaids.org/sites/default/files/media_asset/JC2851_HPV-HIV-cervicalcancer_en.pdf

60. Williamson AL. The Interaction between Human Immunodeficiency Virus and Human Papillomaviruses in Heterosexuals in Africa. *J Clin Med*. 2015;4(4):579-592.

61. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep*. 1992;41(RR-17):1-19.

62. Moodley M, Moodley J, Kleinschmidt I. Invasive cervical cancer and human immunodeficiency virus (HIV) infection: a South African perspective. *Int J Gynecol Cancer*. 2001;11(3):194-197.

63. Moodley M, Mould S. Invasive cervical cancer and human immunodeficiency virus (HIV) infection in KwaZulu-Natal, South Africa. *J Obstet Gynaecol*. 2005;25(7):706-710.

64. Dryden-Peterson S, Bvochora-Nsingo M, Suneja G, Efstathiou JA, Grover S, Chiyapo S, et al. HIV Infection and Survival Among Women With Cervical Cancer. *JCO*. 2016;34(31):3749-3757.

65. Gizaw M, Addissie A, Getachew S, Ayele W, Mitiku I, Moelle U, et al. Cervical cancer patients presentation and survival in the only oncology referral hospital, Ethiopia: a retrospective cohort study. *Infect Agents Cancer*. 2017;12(1):61.

66. MacDuffie E, Bvochora-Nsingo M, Chiyapo S, Balang D, Chambers A, George JM, et al. Five-year overall survival following chemoradiation therapy for locally advanced cervical carcinoma in women living with and without HIV infection in Botswana. *Infect Agents Cancer*. 2021;16(1):55.

67. Simonds HM, Botha MH, Neugut AI, Van Der Merwe FH, Jacobson JS. Five-year overall survival following chemoradiation among HIV-positive and HIV-negative patients with locally advanced cervical carcinoma in a South African cohort. *Gynecol Oncol*. 2018;151(2):215-220.

68. Ferreira MP, Coghill AE, Chaves CB, Bergmann AA, Thuler LC, Soares EA, at al. Outcomes of cervical cancer among HIV-infected and uninfected women treated at the Brazilian National Institute of Cancer (2001–2013. *AIDS*. 2017;31(4):523-531.

69. Mdletshe S, Munkupa H, Lishimpi K. Acute toxicity in cervical cancer HIV-positive vs. HIV-negative patients treated by radical chemo-radiation in Zambia. *Southern African Journal of Gynaecological Oncology*. 2016;8(2):37–41.

70. Grover S, Bvochora-Nsingo M, Yeager A, Chiyapo S, Bhatia R, MacDuffie E, et al. Impact of Human Immunodeficiency Virus Infection on Survival and Acute Toxicities From Chemoradiation Therapy for Cervical Cancer Patients in a Limited-Resource Setting. *Int J Radiat Oncol Biol Phys*. 2018;101(1):201-210.

71. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol*. 2008;26(35):5802-5812.

72. Kotha NV, Williamson CW, Marra KV, McHale M, Mell LK, Mayadev JS. Incomplete cisplatin regimens in chemoradiation and its effect on outcomes for locally advanced cervical cancer. *Int J Gynecol Cancer*. 2022;ijgc-2022-003766.

73. Mamo G, Worku A, Lemma S, Demas T. Cost of Illness of Breast Cancer Patients on Chemotherapy in Addis Ababa Public Hospitals, the Case of Tikur Anbessa Specialized Teaching Hospital-Cross-Sectional Types of Study. *Health Econ Outcome Res*. 2017;03(04).

74. Han K, Milosevic M, Fyles A, Pintilie M, Viswanathan AN. Trends in the utilization of brachytherapy in cervical cancer in the United States. *Int J Radiat Oncol Biol Phys*. 2013;87(1):111-119.

75. Kim YA, Yang MS, Park M, Choi MG, Kim SY, Kim YJ. Brachytherapy utilization rate and effect on survival in cervical cancer patients in Korea. *J Gynecol Oncol.* 2021;32(6):e85.

76. Oaknin A, Rubio MJ, Redondo A, De Juan A, Cueva Bañuelos JF, et al. SEOM guidelines for cervical cancer. *Clin Transl Oncol.* 2015;17(12):1036-1042.

77. Abdel-Wahab M, Bourque JM, Pynda Y, Iżewska J, Van der Merwe D, Zubizarreta E, et al. Status of radiotherapy resources in Africa: an International Atomic Energy Agency analysis. *Lancet Oncol*. 2013;14(4):e168-e175.

78. Wabinga H, Parkin DM, Nambooze S, Amero J. Cancer survival in Kampala, Uganda, 1993-1997. *IARC Sci Publ*. 2011;(162):243-247.

79. Chokunonga E, Borok MZ, Chirenje ZM, Nyabakau AM, Parkin DM. Cancer survival in Harare, Zimbabwe, 1993-1997. *IARC Sci Publ.* 2011;(162):249-255.

80. Sankaranarayanan R, Swaminathan R, Brenner H, Chen K, Chia KS, Chen JG, et al. Cancer survival in Africa, Asia, and Central America: a population-based study. *Lancet Oncol*. 2010;11(2):165-173.

81. Liu YM, Ni LQ, Wang SS, Lv QL, Chen WJ, Ying SP. Outcome and prognostic factors in cervical cancer patients treated with surgery and concurrent chemoradiotherapy: a retrospective study. *World J Surg Oncol*. 2018;16(1):18

82. Elmajjaoui S, Ismaili N, El Kacemi H, Kebdani T, Sifat H, Benjaafar N. Epidemiology and outcome of cervical cancer in national institute of Morocco. *BMC Womens Health.* 2016;16(1):62.

83. Wassie M, Argaw Z, Tsige Y, Abebe M, Kisa S. Survival status and associated factors of death among cervical cancer patients attending at Tikur Anbesa Specialized Hospital, Addis Ababa, Ethiopia: a retrospective cohort study. *BMC Cancer*. 2019;19(1):1221.

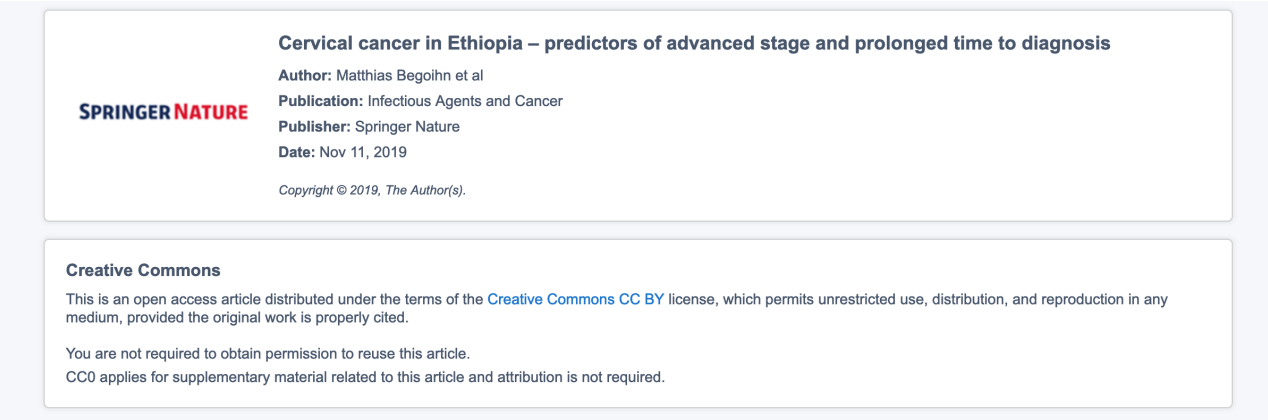
84. Moelle U, Mathewos A, Aynalem A, Wondemagegnehu T, Yonas B, Begoihn M, et al. Cervical Cancer in Ethiopia: The Effect of Adherence to Radiotherapy on Survival. *Oncologist*. 2018;239):1024-1032.

4. Thesen

1. Nur 16,4 % der Patientinnen qualifizierten sich mit einem frühen FIGO-Stadium <2b für eine operative Therapie.
2. Nahezu alle Patientinnen hatten zum Diagnosezeitpunkt Symptome, welche dem Zervixkarzinom zugerechnet werden können. Dies spiegelt einerseits das Fehlen von Screeningmaßnahmen, sowie andererseits das geringe Wissen von Bevölkerung und medizinischem Personal über das Zervixkarzinom wider.
3. Zwischen Beginn der ersten Symptome und histologischer Diagnosestellung vergingen lange Zeiträume (im Median 30 Wochen). Lange Zeiträume zwischen Symptombeginn und histologischer Diagnose, welche insbesondere bei der ländlichen Bevölkerung auftraten waren assoziiert mit fortgeschrittenen FIGO-Stadien.
4. 8,6 % der 1059 Patientinnen hatten einen bekannten positiven HIV-Status gegenüber 23,2 % bekannt negativen und 68,2 % Frauen mit unbekanntem HIV-Status. Diese Frauen waren zum Diagnosezeitpunkt jünger und wurden häufiger in einem fortgeschrittenen Tumorstadium diagnostiziert, weshalb der zielgerichtete Einsatz präventiver Maßnahmen bei HIV-positiven Frauen notwendig ist.
5. Nach Registrierung im Tikur Anbessa Hospital vergingen erneut lange Wartezeiten von 3,8 Monaten im Median bis zum Beginn der Strahlentherapie. In diesem Zeitraum wuchs bei längerer Wartezeit der Anteil an Frauen mit fortgeschrittenem Tumorstadium.
6. Eine unvollständige Strahlentherapie war mit einem schlechteren Gesamtüberleben assoziiert. Häufig wurden Nebenwirkungen der Strahlentherapie als Gründe für einen Therapieabbruch genannt, weshalb es notwendig ist neben supportiven Maßnahmen eine gezieltere Strahlentherapie zu nutzen, z.B. durch den Einsatz intrakavitärer Brachytherapie.
7. Nur 17 % der therapierten Patientinnen mit Zervixkarzinom erhielten eine Chemotherapie trotz eindeutig belegtem Nutzen. Der Einsatz von Chemotherapie muss erweitert werden, um eine leitliniengerechte Therapie zu gewährleisten.
8. Das 1-Jahres- bzw. 2-Jahres-Gesamtüberleben der 1009 therapierten Patientinnen lag mit 83 % bzw. 63 % niedriger als in Ländern des globalen Nordens, war jedoch vergleichbar mit anderen Ländern niedrigen und mittleren Einkommen.

Publikationsteil

Begoihn M, Mathewos A, Aynalem A, Wondemagegnehu T, Moelle U, Gizaw M, Wienke A, Thomssen C, Worku D, Addissie A, Jemal A, & Kantelhardt EJ. Cervical cancer in Ethiopia - predictors of advanced stage and prolonged time to diagnosis. *Infect Agent Cancer*. 2019;14:36. Published 2019 Nov 11. doi:10.1186/s13027-019-0255-4



SPRINGER NATURE

Cervical cancer in Ethiopia – predictors of advanced stage and prolonged time to diagnosis

Author: Matthias Begoihn et al
Publication: Infectious Agents and Cancer
Publisher: Springer Nature
Date: Nov 11, 2019

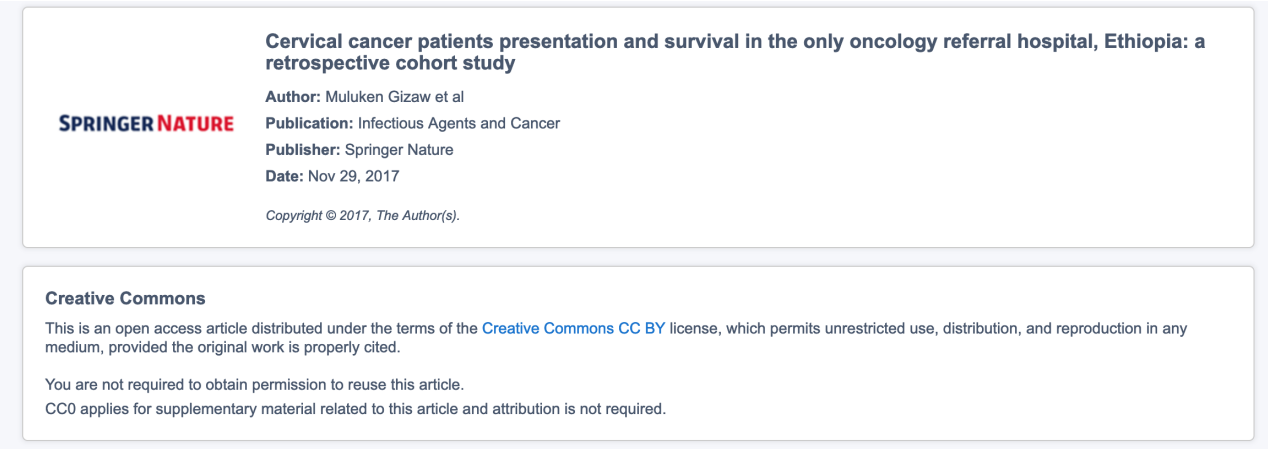
Kantelhardt EJ, Moelle U, **Begoihn M**, Addissie A, Trocchi P, Yonas B, Hezkiel P, Stang A, Thomssen C, Vordermark D, Gemechu T, Gebrehiwot Y, Wondemagegnehu T, Aynalem A, Mathewos A. Cervical cancer in Ethiopia: survival of 1,059 patients who received oncologic therapy. *Oncologist*. 2014;19(7):727-734. doi:10.1634/theoncologist.2013-0326

JOHN WILEY AND SONS LICENSE
TERMS AND CONDITIONS
Jun 11, 2022

This Agreement between University Halle-Wittenberg -- Matthias Begoihn ("You") and John Wiley and Sons ("John Wiley and Sons") consists of your license details and the terms and conditions provided by John Wiley and Sons and Copyright Clearance Center.

License Number	4985480536097
License date	Jan 10, 2021
Licensed Content Publisher	John Wiley and Sons
Licensed Content Publication	The Oncologist
Licensed Content Title	Cervical Cancer in Ethiopia: Survival of 1,059 Patients Who Received Oncologic Therapy
Licensed Content Author	Assefa Mathewos, Abreha Aynalem, Tigeneh Wondemagegnehu, et al
Licensed Content Date	Jun 20, 2014
Licensed Content Volume	19
Licensed Content Issue	7
Licensed Content Pages	8
Type of use	Dissertation/Thesis
Requestor type	Author of this Wiley article
Format	Print and electronic
Portion	Full article
Will you be translating?	No
Title	Cervical Cancer in Ethiopia
Institution name	University Halle Wittenberg
Expected presentation date	Jun 2021
Requestor Location	University Halle-Wittenberg Falckensteinstr 35 Berlin, 10997 Germany Attn: University Halle-Wittenberg
Publisher Tax ID	EU826007151
Total	0.00 EUR

Gizaw M, Addissie A, Getachew S, Ayele W, Mitiku I, Moelle U, Yusuf T, **Begoihn M**, Assefa M, Jemal A, Kantelhardt EJ. Cervical cancer patients presentation and survival in the only oncology referral hospital, Ethiopia: a retrospective cohort study. *Infect Agent Cancer*. 2017;12:61. Published 2017 Nov 29. doi:10.1186/s13027-017-0171-4



SPRINGER NATURE

Cervical cancer patients presentation and survival in the only oncology referral hospital, Ethiopia: a retrospective cohort study

Author: Muluken Gizaw et al
Publication: Infectious Agents and Cancer
Publisher: Springer Nature
Date: Nov 29, 2017

Moelle U, Mathewos A, Aynalem A, Wondemagegnehu T, Yonas B, **Begoihn M**, Addissie A, Unverzagt S, Jemal A, Thomssen C, Vordermark D, Kantelhardt EJ. Cervical Cancer in Ethiopia: The Effect of Adherence to Radiotherapy on Survival. *Oncologist*. 2018;23(9):1024-1032. doi:10.1634/theoncologist.2017-0271

JOHN WILEY AND SONS LICENSE
TERMS AND CONDITIONS
Jun 11, 2022

This Agreement between University Halle-Wittenberg -- Matthias Begoihn ("You") and John Wiley and Sons ("John Wiley and Sons") consists of your license details and the terms and conditions provided by John Wiley and Sons and Copyright Clearance Center.

License Number	4985480922907
License date	Jan 10, 2021
Licensed Content Publisher	John Wiley and Sons
Licensed Content Publication	The Oncologist
Licensed Content Title	Cervical Cancer in Ethiopia: The Effect of Adherence to Radiotherapy on Survival
Licensed Content Author	Eva J. Kantelhardt, Dirk Vordermark, Christoph Thomssen, et al
Licensed Content Date	Mar 23, 2018
Licensed Content Volume	23
Licensed Content Issue	9
Licensed Content Pages	9
Type of use	Dissertation/Thesis
Requestor type	Author of this Wiley article
Format	Print and electronic
Portion	Full article
Will you be translating?	No
Title	Cervical Cancer in Ethiopia
Institution name	University Halle Wittenberg
Expected presentation date	Jun 2021
Requestor Location	University Halle-Wittenberg Falckensteinstr 35 Berlin, 10997 Germany Attn: University Halle-Wittenberg
Publisher Tax ID	EU826007151
Total	0.00 EUR

Begoihn et al. Infectious Agents and Cancer (2019) 14:36
https://doi.org/10.1186/s13027-019-0255-4

Infectious Agents and Cancer

RESEARCH ARTICLE Open Access

Cervical cancer in Ethiopia – predictors of advanced stage and prolonged time to diagnosis

Matthias Begoihn[1], Assefa Mathewos[2], Abreha Aynalem[2], Tigeneh Wondemagegnehu[2], Ulrike Moelle[1], Muluken Gizaw[3,4], Andreas Wienke[3], Christoph Thomssen[1], Dawit Worku[5], Adamu Addissie[3,4], Ahmedin Jemal[6] and Eva Johanna Kantelhardt[1,3*]

Abstract

Introduction: In Ethiopia, most cervical cancer patients present at advanced cancer stages, long time after they experience first symptoms. We investigated possible predictors of long time spans between symptom onset and pathologic diagnosis (patient intervals). We also aimed to seek out predictors for advanced cancer stage diagnosis.

Methods: We conducted a retrospective cohort study among 1575 cervical cancer patients who were registered at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia between September 2008 and September 2012. Cox proportional hazards regression was used to find predictors of long patient intervals. Cumulative odds ordinal logistic regression was used to identify predictors of cancer stage at diagnosis.

Results: Median patient interval was 30 weeks, with the interval substantially longer in patients residing in rural than urban areas. Longer patient intervals were associated with more advanced cancer stages at pathologic diagnosis. HIV-positive women had an almost 1.5 times increased risk of diagnosis at a more advanced stage.

Conclusion: Cervical cancer patients are diagnosed after long time periods leading to advanced stages at diagnosis. Measures to raise awareness about cervical cancer, to increase screening and to shorten the time interval from recognition of symptoms to diagnosis are urgently needed.

Keywords: Cervical cancer, Sub-Saharan Africa, Patient interval, Ethiopia, HIV

Introduction

Cervical cancer incidence and mortality has been drastically reduced in high resource countries during the last decades. This can be largely attributed to the implementation of screening programs for the detection of precancerous lesions and HPV and improved therapy [1, 2]. Yet in low- and middle income countries where access to such measures is limited, cervical cancer remains a significant health problem. The vast majority of an estimated number of 311.000 cervical cancer deaths worldwide occur in less developed regions [3]. In Ethiopia, where almost 6.300 new cases are diagnosed annually, about 4.884 women die from cervical cancer each year. This makes cervical cancer the second-most common cancer in the country, and the second-most deadly cancer among Ethiopian women [4].

One of the most important prognostic factors is stage at diagnosis, linking early-stage diagnosis with better chances of survival [5]; still most cervical cancer patients present at advanced stages in Ethiopia [6]. Studies examining predictors of late and advanced stage presentation of cervical cancer patients in low- and middle-income countries have been scarce [7]. The relationship between HIV-infection and cervical cancer and the question of whether HIV-infection leads to more advanced cancer stages is discussed controversially [8–10]. The timespan between symptom onset and diagnosis has been associated with stage at diagnosis [11], but other studies could not confirm this [12, 13]. However, these studies were

* Correspondence: eva.kantelhardt@uk-halle.de
[1]Department of Gynecology, Martin-Luther-University, Halle (Saale), Germany
[3]Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University, Halle (Saale), Germany
Full list of author information is available at the end of the article

conducted in high-income countries where time to diagnosis is considerably shorter. It is unclear whether these results likewise apply to low-income countries such as Ethiopia, where time to diagnosis is long and patients present at advanced stages. Tragically, in a previous study of a hospital cohort of 1.059 cervical cancer patients receiving oncologic treatment in Addis Ababa, Ethiopia, we found long periods of time between diagnosis and the beginning of cancer treatment. This led to stage-migration and thus decreased chances of survival [6].

In this study, using the same cohort (with the addition of patients who were diagnosed with cervical cancer but never received therapy) we focused on the time between patient reported onset of symptoms and pathological diagnosis (patient interval). The aim of this study was to find predictors for cancer stage at pathological diagnosis and longer patient intervals in Ethiopia. We further hypothesized that longer patient intervals lead to more advanced stages at diagnosis.

Methods

Setting

We conducted a retrospective cohort study among cervical cancer patients who registered at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia between September 2008 and September 2012 as described earlier [6, 14, 15]. TASH is the largest hospital in Ethiopia and the only hospital in the country currently offering radiotherapy – thus, people from all parts of the country were referred there for therapy. Early tumor stages from FIGO Ia - IIa were treated with radical hysterectomy with curative intentions. More advanced tumor stages and cases of unclear surgical margins were treated with external beam radiotherapy. At the time of the study, brachytherapy as recommended according to international guidelines was not available in Ethiopia.

Study population

Ethiopian woman who presented at TASH between September 2008 until September 2012 with a primary diagnosis of invasive cervical cancer were eligible for this study. Of 1655 collected patient files, we used 1575 cases for further analysis. Of these 80 patients were excluded: 42 patients presenting with recurrent disease; two asymptomatic patients who were incidentally diagnosed with cervical cancer; 35 with missing dates regarding pathological diagnosis or symptom onset; one with non-invasive cancer. Since there was no nationwide cervical cancer screening program in place, all women included presented with symptomatic disease. Information regarding patient characteristics, clinical characteristics such as histology, FIGO-Stage, symptoms and waiting times were retrieved from patient files from the oncology and gynecology ward.

Predictor variables

The patients' residency was classified as urban or rural. Patients living in one of the 10 largest cities in Ethiopia were classified as 'urban', while the remaining patients living in smaller cities and villages were classified as 'rural'. HIV-status was subdivided into two groups: positive HIV-status, and negative or unknown HIV-status. Comprehensive HIV-screening at TASH was routinely introduced after September 2011; before this time, only clinically-suspicious patients or patients with a high risk profile (e.g. those with an HIV-positive partner) were screened for HIV. The predictor variables in both models were preselected using variables that were coherent with similar studies [16–18]. Other risk factors commonly examined in regards to both late and advanced stage presentation include socioeconomic status variables such as low education and illiteracy [16–22]. These were not recorded in the patient files at TASH, and thus could not be assessed in this analysis.

Staging

Tumors were staged according to guidelines set by the International Federation of Gynecology and Obstetrics (FIGO) [23]. Stage at primary diagnosis when first seen by a physician was used for further analysis in this study. FIGO-stages were assessed around the date of pathology report. In most cases, a chest X-Ray and abdominal ultrasound followed. If there was an upstaging within 4 weeks after the first staging due to distant metastasis findings or hydronephrosis, the higher FIGO-stage was used. FIGO-stages were later grouped for statistical analysis into stage of FIGO I - IIa (patients receiving primary surgery), FIGO IIb, FIGO III (FIGO IIIa and IIIb) and stage of FIGO IV (IVa and IVb).

Time intervals

Patient interval was defined as the time interval between the date the patient noticed the first symptom and the date of the biopsy report. This interval was used because the date of the first symptom and the date of pathologic diagnosis were widely available, whereas the date of first presentation – i.e. when the patient was first seen by a clinician – was not documented for most patients. Data on symptom onset were abstracted from handwritten documents in the patient files. Patient interval was used as a continuous variable in weeks to avoid loss of power and bias [24, 25].

Statistical analysis

Data were analyzed using SPSS Version 23. A cumulative odds ordinal logistic regression with proportional

odds was conducted to examine the effect of time to diagnosis, HIV-status, place of residence and age on stage at diagnosis. The proportional odds assumption was assessed by a full likelihood ratio test. Odds ratios are presented with their corresponding 95% confidence intervals.

Cox proportional hazards regression was used to evaluate the association between predictors and the patient interval and to calculate hazard ratios (HRs) with 95% confidence intervals. Simple regression analysis was conducted using the predictor variables age, place of residence and HIV-status. For multiple regression analysis, we included all three variables into the model.

Results

Patient characteristics

Mean age was 49 years (SD ±11.6 years). Known HIV-seropositive women presented at a mean age of 39 years, while patients with a negative or unknown HIV-status presented at a mean age of 50 years. One hundred thirty-five of the patients were tested HIV-seropositive (8.6%). Out of the 494 women screened for HIV, 135 women were screened positive and 359 were screened negative. The rest of the women where not screened. Of the HIV-seropositive women, 86.3% were on antiretroviral medication. Close to two thirds of the women came from rural areas. Most woman presented with advanced stages (55.2% stage IIIb or higher). Only 12.1% presented with an early FIGO-stage of I-IIa, making them eligible for surgery (Table 1).

Predictors for longer patient interval

Median patient interval was 30 weeks (range 0–526 weeks). It was shorter for HIV-positive women (25 weeks) compared to women with a negative or unknown HIV-status (30 weeks). Rural women received their pathologic diagnosis after a median time of 32 weeks whereas women from one of the 10 largest cities in Ethiopia were diagnosed after a median time interval of 25 weeks.

Univariate analysis indicated a higher risk for longer patient intervals for women from rural areas compared

Table 1 Demographic and clinical characteristics of the study population according to FIGO Stage at diagnosis ($n = 1575$)

Patient Characteristics	FIGO Stage				
	All Stages	I-IIa	IIb	III	IV
	N	N (%)	N (%)	N (%)	N (%)
All Patients	1575	191 (12.1)	497 (31.6)	731 (46.4)	156 (9.9)
Age (years) (mean + SD) Range 21–93	48,9 ± 11,5	47.9 ± 11.4	49.6 ± 11.9	48.4 ± 11.3	50.9 ± 11.5
Menopausal status					
Premenopausal	344	41 (11.9)	102 (29.7)	175 (50.9)	26 (7.6)
Postmenopausal	1212	148 (12.2)	386 (31.8)	548 (45.2)	130 (10.7)
Unknown	19	2 (10.5)	9 (47.4)	8 (42.1)	0 (0)
Residence					
Rural	976	114 (11.7)	303 (31.0)	465 (47.6)	94 (9.6)
Urban (Biggest 10 Cities)	599	77 (12.9)	194 (32.4)	266 (44.2)	62 (10.4)
HIV Status					
HIV-positive	135	11 (8.1)	37 (27.4)	74 (54.8)	13 (9.6)
negative / unknown	1440	180 (12.5)	460 (31.9)	657 (45.6)	143 (9.9)
Parity (mean + SD) Range 0–17	6.1 ± 3.0	5.6 ± 2.9	6.6 ± 3.1	6.0 ± 3.0	6.5 ± 3.0
Marital Status					
Unmarried	12	2 (6.7)	4 (33.3)	5 (41.7)	1 (8.3)
Early marriage (< 18 years)	1187	146 (12.3)	380 (32.0)	550 (46.3)	111 (9.4)
> 18 years / unknown age	94	20 (21.3)	30 (31.9)	38 (40.4)	6 (6.4)
Unknown Martial Status	282	23 (8.2)	83 (29.4)	138 (48.9)	38 (13.5)
Histology					
Squamous cell carcinoma	1488	170 (11.4)	462 (31.1)	711 (47.8)	145 (9.8)
Adenocarcinoma	66	17 (25.8)	29 (43.9)	12 (18.2)	8 (12.1)
Other	21	4 (19.0)	6 (28.6)	8 (38.1)	3 (14.3)

FIGO International Federation of Gynecology and Obstetrics, *SD* Standard deviation, *HIV* Human immunodeficiency virus
% as proportion among stages

with woman coming from one of the 10 largest cities (HR 1.23; CI 1.11–1.36) (Table 2). Also more likely to be diagnosed later in univariate analysis were younger patients (HR 0.99) and women with a negative or unknown HIV-status (HR 1.19, (CI 1.004–1.43)). After entering all three variables (age, place of residence, HIV-status) in the multiple Cox-Model, the adjusted Hazard Ratio for HIV-status was 1.1 (CI 0.91–1.32) and for age 0.99 (CI 0.99–1). The adjusted Hazard Ratio for place of residence remained 1.23 (CI 1.11–1.36).

Predictors for more advanced stage at diagnosis

We found longer patient intervals associated with more advanced FIGO-stages at diagnosis in the proportional odds model (OR 1.004 (CI 1.002–1.006) p: < 0.001) (Table 3). This means that the odds of being diagnosed in a more advanced stage group increased by 0,004 every week. Patient interval was shortest for early stages (24 weeks for FIGO I-IIa) and longest for advanced stages (35 weeks for FIGO IV) (Fig. 1).

Known HIV-infection was associated with an almost 1.5-fold risk of diagnosis at a more advanced stage compared to those patients with a negative or unknown HIV-status (95% CI 1.05–2.1 $p = 0.025$). Our data suggested no association between place of residence, age and stage at diagnosis.

Symptoms at diagnosis

All patients presented with symptoms related to cervical cancer, with the most common symptoms being abnormal vaginal bleeding, abdominal pain and vaginal discharge (Table 4). Even in early stages I-IIa, 91.1% of patients presented with abnormal vaginal bleeding. Constipation was suggestive of late stage disease: 64% of the patients presenting with constipation were staged IIIb and higher.

Discussion

We found that longer patient intervals increased the risk of advanced stage cervical cancer diagnosis. Previous studies on the effect of longer patient intervals on outcomes like advanced stage and impaired survival presented conflicting results. Consistent with our findings, in the 1980s Fruchter et al. reported an increased risk for presentation at advanced stages of cervical cancer after long patient intervals [11]. In contrast, Tokuda et al. in Japan found no association between patient interval and stage of cervical cancer in the 1990s. However, Japan is a high-resource country and median patient interval was only 30 days [12], differing substantially from the long patient intervals observed in Ethiopia.

We also found that HIV-infection was associated with more advanced cancer stages at time of diagnosis compared to patients with a negative or unknown HIV-status. The association of HIV and HPV is well-known, and previous studies repeatedly linked HIV-infection with a higher prevalence, incidence and persistence of HPV-infection and its progression into precancerous lesions (especially for patients with low CD4 cell counts) [26, 27]. However, the association between HIV and invasive cervical cancer is less clear. Published data indicate a 1.6 to 2.4 increased risk of developing invasive cervical cancer for HIV-positive women [28, 29]. The effect of seroprevalence of HIV on cancer stage at time of diagnosis in comparable settings is similarly hard to establish.

In South-Africa, Lomalisa et al. found that HIV-positive patients with a CD4 count of below 200/mm3 had significantly more advanced tumor stages than HIV-negative women [9]. Fruchter et al. found HIV-positive

Table 3 Predictors for more advanced stage at diagnosis

Predictors	Odds Ratio (95% CI)	*p*-value
Waiting time (weeks)	1.004 (1.002–1.006)	< 0.001
Age (years)	1.004 (0.99–1.01)	0.31
Place of residence		
rural	1.08 (0.89–1.31)	0.42
urban	1	
HIV-Status		
positive	1.48 (1.05–2.1)	0.025
Negative / unknown		

CI Confidence interval, *HIV* Human immunodeficiency virus

Table 2 Predictors for longer patient interval (time between symptom onset and pathologic diagnosis)

Predictor	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	*p*-value
Age (years)	0.99 (0.99–1)	0.99 (0.99–1)	0.7
Place of residence			
Rural	1.23 (1.11–1.36)	1.23 (1.11–1.36)	< 0.001
Urban			
HIV-Status			
positive	1.19 (1.004–1.43)	1.1 (0.91–1.32)	0.29
Negative/unknown	1	1	

HR Hazard ratio, *CI* Confidence interval, *HIV* Human immunodeficiency virus

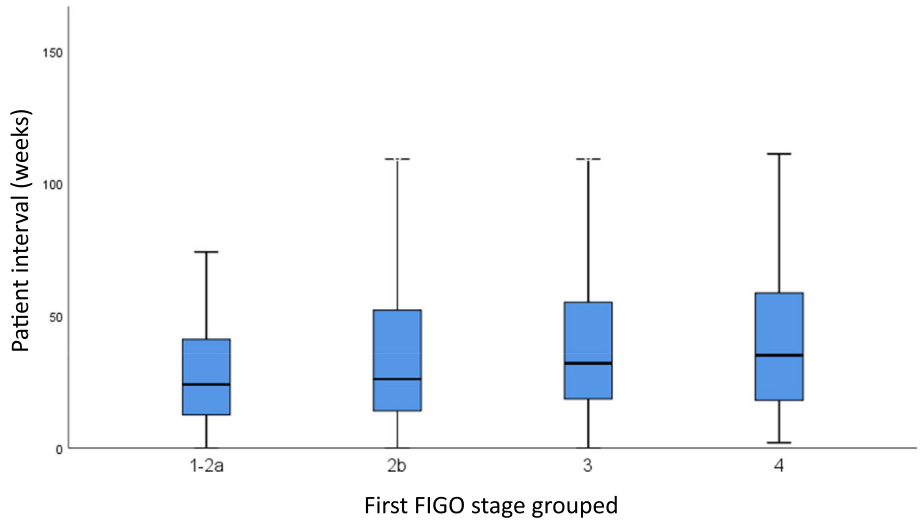


Fig. 1 Box-plot showing median patient interval (time between symptom onset and pathologic diagnosis in weeks) with 25th and 75th percentile by FIGO stage group

patients to be at elevated risk for advanced cervical cancer diagnoses in univariate analysis. That said, their observed study group was small and statistical significance ceased after adjusting their model for other variables [8]. Moodley et al. found advanced stages among both HIV-positive and -negative patients with no association between HIV-status and stage [10]. On average HIV-seropositive women in our study presented 11 years younger than patients with a negative or unknown HIV-status [14]; this is consistent with the previous scientific literature where HIV-positive women presented 10–15 years earlier than HIV-negative women [10, 30]. The association of HIV-infection and advanced stage presentation of cervical cancer could potentially be explained by the HIV-associated immunodeficiency leading to a more rapid cancer growth, although other authors attribute this to molecular interactions between HIV and HPV [31–33]. Ibrahim et al. in Sudan identified high age and rural residence as predictors for advanced stage presentation [16]. Findings from similar studies in Morocco and South India include socioeconomic factors such as low education and illiteracy [17, 19].

In our study, women from rural areas tended to have longer patient intervals. This may be attributable to a low awareness of cervical cancer and its associated symptoms or the lack of health facilities and skilled personnel in rural parts of the country. Macleod et al. reported a lack of awareness and a misinterpretation of the seriousness of symptoms as the main risk factor for long patient intervals [20]. Fear of finding cancer and socioeconomic factors like illiteracy were other common themes among comparable studies [11, 17, 21].

In multivariate analysis, rural origin was associated but both age and HIV-status were not associated with long patient intervals in our study. Other factors that presumably influence the length of the patient interval include financial and logistic factors including delays in health care service.

We observed long time periods of median 25 to 35 weeks between women noticing the first symptom and pathological diagnosis among all stages, increasing with FIGO-stage. A comparable study in Nepal found shorter patient intervals of median 22 weeks [18]. Even in early stages, women were often diagnosed after many weeks or months of experiencing symptoms of cervical cancer such as abnormal vaginal bleeding, pain and vaginal discharge. After pathological diagnosis, patients often had to wait months until radiotherapy started, which further increased the risk of cancer progression [6].

Table 4 Intensity of common symptoms when first seen by a physician among cervical cancer patients ($n = 1575$)

Symptoms	Intensity of symptoms									
	None		Mild		Moderate		Severe		Unknown	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Vaginal bleeding	115	(7.3)	404	(25.7)	977	(62.0)	74	(4.7)	5	(0.3)
Pelvic pain	442	(28.1)	213	(13.5)	858	(54.5)	57	(3.6)	5	(0.3)
Vaginal discharge	424	(26.9)	331	(21.0)	814	(51.7)	–		6	(0.4)
Constipation	1267	(80.4)	101	(6.4)	197	(12.5)	5	(0.3)	5	(0.3)

The key strength of this study is the large sample size with patients coming from all over Ethiopia. There are, however, certain limitations we need to acknowledge. Data regarding patient and tumor characteristics and dates used for the calculation of patient interval were extracted from handwritten medical records. These dates relied on self-reporting from patients who might have been subjected to recall bias. We do not know how well women remembered the date of symptom onset and how meticulously it was documented. Secondly, women who were symptomatic for a long time but never presented to a health care professional may have died at advanced stages without ever being diagnosed at TASH and thus did not appear in our study. Hence, such a selection bias might falsely result in favorable data, particularly for patients with advanced cancer stages. Since the date of first presentation to a health care professional was not available for many patients, it was not possible to identify precisely at which stages of the diagnostic pathway these delays occur. Some patients may have been clinically diagnosed earlier and then had to wait until referral for pathological diagnosis – yet for the patients for whom all data were available, this interval did not vary substantially between tumor stages and residence. Qualitative research is needed to identify the impediments to diagnosis which lead to long patient intervals and more advanced stage presentation.

Previous studies found that efforts in down-staging helped to significantly increase overall survival. A three-year program in rural Tanzania with the aim of down-staging cancer through proactive visits from trained health aides into people's homes showed favorable results [34]. One study conducted in rural India found that a cervical cancer education group effectively reduced the ratio of advanced stage diagnoses and increased the number of women diagnosed at early tumor stages [35]. However, awareness of cervical cancer and knowledge of risk factors, signs and symptoms are still low among women in Ethiopia and other African countries [36–38]. In Malaysia, advanced cervical cancer presentation (stages III and IV) dropped from 60 to 26% within 4 years after a program was introduced, focusing on training health staff and strengthening public awareness through the use of pamphlets and posters in clinics and hospitals [39].

Prevention and down-staging programs could be integrated in HIV/AIDS care programs and other preexisting healthcare infrastructures like it has been successfully implemented in Zambia [40, 41]. Alongside an increased coverage of HPV vaccination and screening, such initiatives could help reduce cervical cancer mortality and incidence worldwide.

Conclusion

Our results support the hypothesis that long patient intervals lead to more advanced cervical cancer stages at pathologic diagnosis. Especially rural women tended to be diagnosed late and need to be addressed through awareness programs. HIV-postive women were at elevated risk of advanced tumor presentation; this should encourage efforts of the government to implement specific screening programs for HIV positive women. In addition to the current government efforts to implement nationwide screening programs, information about signs and symptoms of the disease should be spread.

Abbreviations

CI: Confidence Intervals; FIGO: International Federation of Gynecology and Obstetrics; HIV: Human Immunodeficiency Virus; HPV: Human Papilloma Virus; HR: Hazard Ratio; TASH: Tikur Anbessa Specialized Hospital

Acknowledgements

Authors would like to thank the staff members of Tikur Anbessa Specialized Hospital Radiotherapy Center who treated and provided care for all cervical cancer patients. We also greatful to Mrs. Tinsae and Mrs. Tigist for obtaining the follow-up data and Mrs. Mulu and Mr. Neme for collecting the patient files.

Authors' contributions

MB performed statistical analysis and drafted the manuscript. EK, AJ, MG, UM and AW participated in designing the study, analysis, reviewing and editing the final manuscript and contributed to the discussion. UM and MB collected the data at TASH in Addis Ababa, Ethiopia. All the authors were involved in drafting of the manuscript and read and approved the final form of the manuscript.

Funding

This study was supported by the Federal Ministry of Research and Education of.
Germany, grant 01DG12006.

Availability of data and materials

The datasets analyzed are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical approval was obtained from the institutional review board of the College of Health Sciences, Addis Ababa University and Martin-Luther-University, Halle Germany.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Gynecology, Martin-Luther-University, Halle (Saale), Germany. [2]Radiotherapy Center, School of Medicine, Addis Ababa University, Addis Ababa, Ethiopia. [3]Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University, Halle (Saale), Germany. [4]Department of Preventive Medicine School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia. [5]Department of Gynecology, School of Medicine Addis Ababa University, Addis Ababa, Ethiopia. [6]Department of Intramural Research, American Cancer Society, Atlanta, Georgia.

Received: 9 August 2019 Accepted: 5 November 2019
Published online: 11 November 2019

References

1. Denny L, et al. Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries. Lancet. 2017;389(10071):861–70.

2. Aranda S, Berkley S, Cowal S, Dybul M, Evans T, Iversen K, Moeti M, Osotimehin B, Peterson S, Piot P, Purandare CN, Sidibé M, Trimble T, Tsu VD. Ending cervical cancer: a call to action. Int J Gynecol Obstet. 2017;138:4–6.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
4. Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. ICO/IARCInformation Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in the World. Summary Report 22 January 2019. Available at: https://www.hpvcentre.net/statistics/reports/XWX.pdf. Accessed 10 June 2019.
5. Waggoner SE. Cervical cancer. Lancet. 2003;361(9376):2217–25.
6. Kantelhardt EJ, Moelle U, Begoihn M, et al. Cervical Cancer in Ethiopia: survival of 1,059 patients who received oncologic therapy. Oncologist. 2014; 19(7):727–34.
7. Finocchario-Kessler S, Wexler C, Maloba M, Mabachi N, Ndikum-Moffor F, Bukusi E. Cervical cancer prevention and treatment research in Africa: a systematic review from a public health perspective. BMC Womens Health. 2016;16(1):29.
8. Fruchter RG, Maiman M, Arrastia CD, Matthews R, Gates EJ, Holcomb K. Is HIV infection a risk factor for advanced cervical cancer? J Acquir Immune Defic Syndr Hum Retrovirol. 1998;18(3):241–5.
9. Lomalisa P, Smith T, Guidozzi F. Human immunodeficiency virus infection and invasive cervical cancer in South Africa. Gynecol Oncol. 2000;77(3):460–3.
10. Moodley M, Moodley J, Kleinschmidt I. Invasive cervical cancer and human immunodeficiency virus (HIV) infection: a south African perspective. Int J Gynecol Cancer. 2001;11(3):194–7.
11. Fruchter RG, Boyce J. Delays in diagnosis and stage of disease in gynecologic cancer. Cancer Detect Prev. 1981;4(1–4):481–6.
12. Tokuda Y, Chinen K, Obara H, Joishy SK. Intervals between symptom onset and clinical presentation in cancer patients. Intern Med. 2009; 48(11):899–905.
13. Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, Hamilton W, Hendry A, Hendry M, Lewis R, Macleod U. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. Br J Cancer. 2015;112(s1):S92.
14. Gizaw M, Addissie A, Getachew S, Ayele W, Mitiku I, Moelle U, Yusuf T, Begoihn M, Assefa M, Jemal A, Kantelhardt EJ. Cervical cancer patients presentation and survival in the only oncology referral hospital, Ethiopia: a retrospective cohort study. Infect Agents Cancer. 2017;12(1):61.
15. Moelle U, Mathewos A, Aynalem A, Wondemagegnehu T, Yonas B, Begoihn M, Addissie A, Unverzagt S, Jemal A, Thomssen C, Vordermark D, Kantelhardt EJ. Cervical Cancer in Ethiopia: the effect of adherence to radiotherapy on survival. Oncologist. 2018;23(9):1024–32.
16. Ibrahim A, Rasch V, Pukkala E, Aro AR. Predictors of cervical cancer being at an advanced stage at diagnosis in Sudan. Int J Women's Health. 2011;3:385.
17. Ouasmani F, Hanchi Z, Haddou Rahou B, Bekkali R, Ahid S, Mesfioui A. Determinants of patient delay in seeking diagnosis and treatment among Moroccan women with cervical cancer. Obstet Gynecol Int. 2016;2016: 4840762.
18. Gyenwali D, Khanal G, Paudel R, Amatya A, Pariyar J, Onta SR. Estimates of delays in diagnosis of cervical cancer in Nepal. BMC Womens Health. 2014; 14(1):29.
19. Kaku M, Mathew A, Rajan B. Impact of socio-economic factors in delayed reporting and late-stage presentation among patients with cervix cancer in a major cancer hospital in South India. Asian Pac J Cancer Prev. 2008;9(4): 589–94.
20. Macleod U, Mitchell ED, Burgess C, Macdonald S, Ramirez AJ. Risk factors for delayed presentation and referral of symptomatic cancer: evidence for common cancers. Br J Cancer. 2009;101(S2):S92.
21. Ashing-Giwa KT, Gonzalez P, Lim JW, Chung C, Paz B, Somlo G, Wakabayashi MT. Diagnostic and therapeutic delays among a multiethnic sample of breast and cervical cancer survivors. Cancer. 2010;116(113):3195–204.
22. Forbes LJ, Warburton F, Richards MA, Ramirez AJ. Risk factors for delay in symptomatic presentation: a survey of cancer patients. Br J Cancer. 2014; 111(3):581.
23. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynecol Obstet. 2009;105(2):103–4.
24. Weller D, Vedsted P, Rubin G, Walter FM, Emery J, Scott S, Campbell C, Andersen RS, Hamilton W, Olesen F, Rose P. The Aarhus statement: improving design and reporting of studies on early cancer diagnosis. Br J Cancer. 2012;106(7):1262.
25. Neal RD. Do diagnostic delays in cancer matter? Br J Cancer. 2009;101(S2): S9.
26. De Vuyst H, Lillo F, Broutet N, Smith JS. HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. Eur J Cancer Prev. 2008;17(6):545–54.
27. Denslow SA, Rositch AF, Firnhaber C, Ting J, Smith JS. Incidence and progression of cervical lesions in women with HIV: a systematic global review. Int J STD AIDS. 2014;25(3):163–77.
28. Newton R, Ziegler J, Beral V, Mbidde E, Carpenter L, Wabinga H, Mbulaiteye S, Appleby P, Reeves G, Jaffe H. A case-control study of human immunodeficiency virus infection and cancer in adults and children residing in Kampala, Uganda. Int J Cancer. 2001;92(5):622–7.
29. Mbulaiteye SM, Katabira ET, Wabinga H, Parkin DM, Virgo P, Ochai R, Workneh M, Coutinho A, Engels EA. Spectrum of cancers among HIV-infected persons in Africa: the Uganda AIDS-Cancer registry match study. Int J Cancer. 2006;118(4):985–90.
30. Moodley M, Mould S. Invasive cervical cancer and human immunodeficiency virus (HIV) infection in KwaZulu-Natal, South Africa. J Obstet Gynaecol. 2005;25(7):706–10.
31. Stanley M. Immune responses to human papillomavirus. Vaccine. 2006;24: S16–22.
32. Boccalon M, Tirelli U, Sopracordevole F, Vaccher E. Intra-epithelial and invasive cervical neoplasia during HIV infection. Eur J Cancer. 1996;32(13): 2212–7.
33. Clarke B, Chetty R. Postmodern cancer: the role of human immunodeficiency virus in uterine cervical cancer. Mol Pathol. 2002;55(1):19.
34. Ngoma T, Mandeli J, Holland JF. Downstaging cancer in rural Africa. Int J Cancer. 2015;136(12):2875–9.
35. Jayant K, Rao RS, Nene BM, Dale PS, Nandakumar A. Improved survival in cervical cancer cases in a rural Indian population. Br J Cancer. 1996;74(2): 285.
36. Birhanu Z, Abdissa A, Belachew T, Deribew A, Segni H, Tsu V, Mulholland K, Russell FM. Health seeking behavior for cervical cancer in Ethiopia: a qualitative study. Int J Equity Health. 2012;11(1):83.
37. Getahun F, Mazengia F, Abuhay M, Birhanu Z. Comprehensive knowledge about cervical cancer is low among women in Northwest Ethiopia. BMC Cancer. 2013;13(1):2.
38. Shiferaw S, Addissie A, Gizaw M, Hirpa S, Ayele W, Getachew S, Kantelhardt EJ, Assefa M, Jemal A. Knowledge about cervical cancer and barriers toward cervical cancer screening among HIV-positive women attending public health centers in Addis Ababa city, Ethiopia. Cancer Med. 2018;7(3):903–12.
39. Devi BCR, Tang TS, Corbex M. Reducing by half the percentage of late-stage presentation for breast and cervix cancer over 4 years: a pilot study of clinical downstaging in Sarawak, Malaysia. Ann Oncol. 2007;18(7):1172–6.
40. Mwanahamuntu MH, Sahasrabuddhe VV, Kapambwe S, Pfaendler KS, Chibwesha C, Mkumba G, Mudenda V, Hicks ML, Vermund SH, Stringer JS, Parham GP. Advancing cervical cancer prevention initiatives in resource-constrained settings: insights from the cervical Cancer prevention program in Zambia. PLoS Med. 2011;8(5):e1001032.
41. Mwanahamuntu MH, Sahasrabuddhe VV, Pfaendler KS, Mudenda V, Hicks ML, Vermund SH, Stringer JS, Parham GP. Implementation of 'see-and-treat'cervical cancer prevention services linked to HIV care in Zambia. AIDS (London, England). 2009;23(6):N1.

Publisher's Note

The Oncologist®

Global Health and Cancer

Cervical Cancer in Ethiopia: Survival of 1,059 Patients Who Received Oncologic Therapy

Eva Johanna Kantelhardt,[a,b] Ulrike Moelle,[a] Matthias Begoihn,[a] Adamu Addissie,[c] Pietro Trocchi,[b] Bekuretsion Yonas,[d] Petros Hezkiel,[e] Andreas Stang,[b,g] Christoph Thomssen,[a] Dirk Vordermark,[c] Tufa Gemechu,[d] Yirgu Gebrehiwot,[e] Tigeneh Wondemagegnehu,[f] Abreha Aynalem,[f] Assefa Mathewos[f]

[a]Department of Gynaecology and [b]Institute of Clinical Epidemiology, Martin Luther University, Halle an der Saale, Germany; [c]School of Public Health, Departments of [d]Pathology and [e]Gynaecology, and [f]Radiotherapy Center, School of Medicine, Addis Ababa University, Addis Ababa, Ethiopia; [g]Department of Epidemiology, School of Public Health, Boston University, Boston, Massachusetts, USA

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

Key Words. Uterine cervical neoplasms • Africa • Ethiopia • Survival • Prognosis

Abstract

Background. Almost 500,000 women are newly diagnosed with cervical cancer (CC) every year, the majority from developing countries. There is little information on the survival of these patients. Our primary objective was to evaluate consecutive CC patients presenting over 4 years at the only radiotherapy center in Ethiopia.

Methods. All patients with CC from September 2008 to September 2012 who received radiotherapy and/or surgery were included (without brachytherapy). Vital status was obtained through telephone contact or patient cards.

Results. Of 2,300 CC patients, 1,059 patients with standardized treatment were included. At the end of the study, 249 patients had died; surviving patients had a median follow-up of 16.5 months; the 10% and 90% percentiles were 3.0 and 32.7 months, respectively. Mean age was 49 years (21–91 years). The majority of patients presented with International Federation of Gynecology and Obstetrics stage IIb–IIIa (46.7%). Because of progression during the waiting time (median 3.8 months), this proportion declined to 19.3% at the beginning of radiotherapy. The 1- and 2-year overall survival probabilities were 90.4% and 73.6%. If assuming a worst-case scenario (i.e., if all patients not available for follow-up after 6 months had died), the 2-year survival probability would be 45.4%.

Conclusion. This study gives a thorough 4-year overview of treated patients with CC in Ethiopia. Given the limited treatment availability, a relatively high proportion of patients survived 2 years. More prevention and early detection at all levels of the health care system are needed. Increasing the capacity for external-beam radiation as well as options for brachytherapy would facilitate treatment with curative intention. ***The Oncologist*** 2014;19:727–734

Implications for Practice: This study analyzes 1,059 patients from Ethiopia with newly diagnosed cervical cancer who were treated by radiotherapy in the country's only oncologic referral center. Overall survival after 2 years was considerably high (74%) compared with data from African cancer registries, underlining the usefulness of radiotherapy. The survival was still lower than that of patients from higher-resource settings, probably because of the lack of brachytherapy. Therefore, brachytherapy for cervical cancer patients should be of high priority. Patients with earlier stages of disease had better outcome compared with those with later stages. Awareness and early detection programs are needed in the Ethiopian setting.

Introduction

Every year, almost 500,000 women worldwide are estimated to be newly diagnosed with cancer of the cervix uteri [1]. The majority of cases are found in developing countries; in Africa almost 60,000 women die of the disease each year [2]. In 2004, cervical cancer contributed to 3.4 million years of life lost (YLL) worldwide and was the greatest single cause of YLL from cancer in women from low-income countries [3]. This mainly reflects the absence of national cancer control programs, including vaccination, screening, and early detection, in most African countries. Cervical cancer accounts for 22% of cancer deaths in women aged 15–59 years, making it a symbol for global health disparity; it burdens young women from the poorest countries and the most disadvantaged populations [4, 5]. Cancer patients in sub-Saharan Africa tend to present with advanced disease [6]. Despite this, in 2010 radiotherapy was available in only 23 of 52 African countries—mostly in the northern and southern states of the continent. Brachytherapy was available in only 20 countries [7]. Only a small amount of epidemiological data on cervical cancer is currently available [8]; only five African cancer registries were included in the World Health

Correspondence: Eva Johanna Kantelhardt, M.D., Department of Gynaecology and Institute of Clinical Epidemiology, Ernst-Grube Strasse 40, 06097 Halle an der Saale, Germany. Telephone: 49-345-557-1847; E-Mail: eva.kantelhardt@medizin.uni-halle.de Received August 20, 2013; accepted for publication May 8, 2014; first published online in ***The Oncologist*** *Express* on June 20, 2014. 1083-7159/2014/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2013-0326

Organization publication "Cancer Incidence in Five Continents, Volume IX" [9]. Variations in incidence are expected within countries between rural and urban settings [10], as well as between different regions [11]. Research on cancer in Africa is increasingly being facilitated through various initiatives (e.g., the Global Initiative for Cancer Registry Development in Low- and Middle-Income Countries and the African Organisation for Research and Training in Cancer) [12].

Ethiopia is the second most populated country in sub-Saharan Africa, with more than 42 million females [13]. Ethiopia is one of the least urbanized countries in the world, with only 16% of the population living in urban areas [14]. There are an estimated 7,000 new cases of cervical cancer in Ethiopia per year; nearly 5,000 people are estimated to die of the disease per year [15]. Public oncological treatment in Ethiopia, including radiotherapy, is limited to the Radiotherapy Center at Tikur Anbessa University Hospital, which is staffed by four radiation oncologists. Treatment options for patients with cervical cancer are radical hysterectomy (Wertheim operation) when in the early stages, at the Department of Gynaecology at Tikur Anbessa Hospital. External-beam radiation can be given combined with chemotherapy at the Radiotherapy Department. Brachytherapy is not available in Ethiopia. When attending the hospital, patients first have to register at the Radiotherapy Department for an appointment with the radiation oncologist. At this appointment, evaluation and planning of radiotherapy is performed by the radiation oncologist. Thereafter, patients receive an appointment to start radiotherapy. Because of huge patient loads, a considerable amount of time may pass between these appointments. Patients with acute bleeding receive priority for appointments for emergency radiation. Little is known about the outcome of cervical cancer patients who receive therapy in such settings with limited resources. Recent publications point toward the need for more epidemiological data on noncommunicable diseases, including cancer, for example from cohort studies [16, 17].

The primary aim of this study was to estimate the overall survival of women with cancer of the cervix uteri whose diagnosis and treatment by surgery and/or radiotherapy at the Radiotherapy Center Addis Ababa took place between September 10, 2008 and September 11, 2012.

Materials and Methods

Patients and Methods

Women with histologically verified cancer of the cervix uteri (International Classification of Disease-Oncology (ICD-O-3) codes C53.0–9) who were diagnosed and treated between September 10, 2008 and September 11, 2012 at the Radiotherapy Center at Tikur Anbessa Hospital in Addis Ababa, Ethiopia, were included in the study. Treatment consisted of radiotherapy and/or surgery. All patient characteristics, tumor characteristics, and information concerning therapy and outcome were extracted from the patients' files. Waiting time was calculated between the date of the first presentation at the hospital and start of radiotherapy. All patients with telephone numbers available were contacted by telephone. Information on the date of last contact and survival status was obtained by telephone from the patients or—in case of death—from relatives. If patients or relatives were not reached by telephone, the last date of personal contact was taken from the patients' files.

Staging

Tumors were classified according to the International Federation of Gynecology and Obstetrics (FIGO) staging system [18]. The FIGO stage was based on clinical examination by at least one of the four radiation oncologists from the Radiotherapy Center (by authors A.M., T.W., and A.A.) and was documented in the patients' files. The FIGO stage at first presentation to the hospital was used for further analysis. In cases of discrepancy between examinations, another radiation oncologist was consulted. In a few cases of additional radiologic or sonographic detection of hydronephrosis around the time of diagnosis, the FIGO stage was classified as stage IIIb; in cases of distant metastasis, the FIGO stage was classified as stage IVb (by authors U.M. and M.B.). Patients with lack of findings on routinely performed chest x-ray and abdominal ultrasound were considered "free of distant metastasis." The histological results were documented according to written notes from pathology reports.

Treatment Modalities

Patients with cervical cancer were referred from all over Ethiopia to Tikur Anbessa Hospital for radiotherapy. This hospital has one cobalt-60 teletherapy unit. Patients with early-stage disease residing in Addis Ababa were referred for surgery as well. The surgical treatment was radical hysterectomy with pelvic lymphadenectomy (Wertheim). This surgery was performed in cases of FIGO stages Ia, Ib, and IIa. Tikur Anbessa Hospital is the only hospital in Ethiopia regularly performing Wertheim surgery and the only facility administering combination radiochemotherapy. Patients with a FIGO stage lower than IIb and clear surgical margins and negative lymph nodes did not receive radiotherapy. Also, patients with renal failure did not receive radiotherapy.

Adjuvant, radical, and palliative radiotherapy were applied in two phases. In the first phase, opposing-field techniques (anterior-posterior/posterior-anterior) were used, and in the second phase, four-field box techniques were applied. Typically, opposing fields in the first phase were 20–22 by 20–22 cm in size and included the gross tumor volume and the pelvic lymph nodes (upper border: L5/S1, lower border: 2–3 cm below palpable tumor, lateral borders to include inguinal nodes). In the second-phase, boost series directed only at the gross tumor volume, the typical size of an anterior field in the four-field box technique was 12 by 14 cm.

Adjuvant radiotherapy was given to patients after surgery without clear surgical margins or with positive lymph nodes and/or parametrium involvement. The patients received 40 Gy in 20 fractions of 2.0 Gy within 4–5 weeks in the first phase. Depending on tumor response, adverse effects, and compliance of the patients, a boost dose of 20–26 Gy was applied in 10–13 fractions of 2.0 Gy within 2–3 weeks in the second phase. In cases of FIGO stage IIb or IIIa, as well as cases of FIGO stage less than IIb without surgery, primary radical radiotherapy was given. The patients received 46 Gy in 23 fractions of 2.0 Gy within 5–6 weeks in the first phase and 26 Gy in 13 fractions within 2–4 weeks in the second phase. Patients with FIGO stage IIIb or 4a without bilateral hydronephrosis or clinical fistula

were given palliative radiotherapy with a larger dose per fraction: 32 Gy in 8 fractions of 4.0 Gy within 4 weeks in the first phase followed by a second phase of 18 Gy (6 fractions of 3.0 Gy) or 12 Gy (4 fractions of 3.0 Gy) within 2–3 weeks. In cases of FIGO stage IVa or IIIb with bilateral hydronephrosis, stage IVa with clinical fistula, or FIGO stage IVb, the patients received two single fractions of 10 Gy each, and depending on response, performance status, and site of metastasis, they received additional radiotherapy or palliative chemotherapy.

The waiting time for application of single-fraction radiotherapy was short (1–2 days), and therefore this concept was also applied for FIGO stage I–II patients who were unable to stay in Addis Ababa for longer periods of time because of their socioeconomic background. This applied to 12% of patients with FIGO stage Ia–IIa and 15% of patients with FIGO stage IIb–IIIa. Hemostatic radiotherapy (12 Gy in 4 fractions) was administered independently of FIGO stage because of massive vaginal bleeding and decline in hematocrit. In curative concepts, chemotherapy was recommended simultaneous with curative radiotherapy or rarely neoadjuvant to surgery (cisplatin, 60 mg/m^2, 3–6 cycles). Palliative chemotherapy with cisplatin and 5-fluorouracil (50 mg/m^2, 6 cycles) was recommended to patients with FIGO stage IIIb–IVb. Because of the limited availability of the substances and the financial limitations of the patients, chemotherapy was not administered on a regular basis.

Statistical Analysis

The primary endpoint of this study was overall survival. Person time equaled the time from the date of pathologic diagnosis to death or to closing date for follow-up (August 7, 2013), whichever came first. Women were right-censored at the date of last contact before the closing date. The survival probabilities in months were estimated using the Kaplan-Meier method. The 95% confidence intervals at year 2 are shown. Kaplan-Meier estimates were compared using the log-rank test. Analyses were conducted using SPSS Statistics, version 19 (SPSS software, IBM Corp., Armonk, NY, http://www-01.ibm.com/software/analytics/spss/) and SAS (SAS Institute, Inc., Cary, NC, http://www.sas.com), version 9.3. The median follow-up time for surviving patients was 16.5 months (range, 0.1–53.0 months). In the first analysis, we assumed right censoring to be unrelated to the risk of distant metastasis. Worst-case analysis assumed that all patients who were not available for follow-up after 6 months had died.

Ethics

For this study, ethical approval was obtained from the Institutional Review Boards of Addis Ababa University School of Medicine and Martin Luther University Halle. The study was conducted without individual informed consent because the study relied on retrospective data collected as part of routine patient care.

Results

Description of the Study Population

Between September 9, 2008 and September 11, 2012, an estimated 2,300 patients with cancer of the cervix uteri were registered at the Radiotherapy Center. This includes 111 patients who received surgery for the cancer. Of those, 1,837 were seen by the radiation oncologist, and radiotherapy was planned. The estimated number of patients who received radiotherapy was 1,400. Of those, 1,012 patient files could be retrieved. An additional 47 patients who received only surgery for early-stage cervical cancer were included in the study. Note that an estimated 900 patients who registered never received any therapy (Fig. 1).

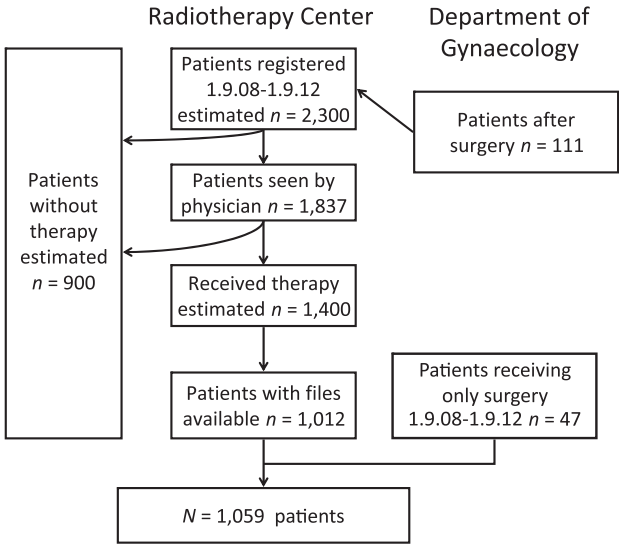


Figure 1. CONSORT diagram. Patients diagnosed with cancer of the uterine cervix included in this study are a subgroup of all who presented at the Radiotherapy Center or Department of Gynecology of Tikur Anbessa University Hospital, Addis Ababa.

Patient Characteristics

Most patients came from rural areas (56.5%). The largest group of patients were 40–49 years old (30.9%). The majority of patients (78.1%) were postmenopausal. The mean number of children was 6.0, with 10% and 90% percentiles of 2 and 10, respectively. Many women reported only one lifetime sexual partner (52.7%), as well as marriage before the age of 18 (83.9%). The proportion of women using contraceptives was 31.1%. A total of 9.4% were known to be HIV-positive. The Eastern Cooperative Oncology Group performance status 1 at first presentation was common (57.8%). The largest group of patients presented with FIGO stage IIb–IIIa (46.7%) and squamous cell carcinoma (93.4%) (Table 1).

An important piece of baseline information is change in FIGO stage between pathological diagnosis and the start of radiotherapy, during which time a considerable number of patients died while waiting for treatment. However, information about these patients was not available. Because of the huge patient load, the median waiting time was 1.8 months between first registration at the Radiotherapy Center and the first appointment with the radiation oncologist (10th and 90th percentiles were 0.2 and 5.2 months, respectively). The median waiting time between the appointment with the radiation oncologist and the start of radiotherapy was 0.2 months for emergency radiotherapy, 1.7 months for curative radiotherapy, and 2.3 months for palliative radiotherapy (supplemental online Fig. 1). The proportion of patients with advanced stage IIIb and above increased between the

Table 1. Basic demographic data of the 1,059 patients when first seen by a physician

Characteristics	Number	Proportion (%)
Total population	1,059	100
Place of origin		
Urban (10 biggest cities)	461	43.5
Only Addis Ababa	311	29.4
Rural	598	56.5
Age (years)		
<30	28	2.6
30–39	178	16.8
40–49	326	30.8
50–59	287	27.1
≥60	240	22.7
Menopausal status		
Premenopausal	221	20.9
Postmenopausal	827	78.1
Unknown	11	1.0
Marriage		
Early (≤18 years)	888	83.9
After age 18	67	6.3
Unmarried	10	0.9
Unknown	94	8.9
Parity (mean and standard deviation; information available for 97.8% patients)	5.99 ± 3.137	
Sexual partners		
None	2	0.2
One	558	52.7
Few (2–3)	157	14.8
Multiple (>3)	233	22.0
Unknown	109	10.3
Contraceptives		
Hormonal (pill, injectable, implant)	293	27.7
Nonhormonal (IUD, condoms, tubal ligation)	17	1.6
Combined	19	1.8
None	677	63.9
Unknown	53	5.0
HIV status		
Positive	100	9.4
Negative/unknown/not screened	959	90.6
First ECOG		
Fully active (ECOG 0)	5	0.5
Lightly restricted (ECOG 1)	612	57.8
Unable to work (ECOG 2)	315	29.7
Limited self-care >50% in bed (ECOG 3)	117	11.0
No self-care, bedbound (ECOG 4)	10	0.9
Stage (FIGO)		
Ia–IIa	174	16.4
IIb–IIIa	495	46.7
IIIb–IVa	355	33.5
IVb	7	0.7
Recurrence	28	2.7
Histology		
Squamous	989	93.4
Keratinizing	302	28.5
Nonkeratinizing	348	32.9
Not specified	339	32.0
Adenocarcinoma	54	5.1
Adenosquamous carcinoma	11	1.0
Small cell	3	0.3
Other/unspecified/unknown	2	0.2
Grade		
Well differentiated	76	7.2
Moderately differentiated	94	8.9
Poorly differentiated	59	5.5
Undifferentiated	7	0.7
Not done	823	77.7

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

appointment with the radiation oncologist (44.2%) and the start of radiotherapy (68.3%) (Fig. 2).

Treatment Modalities

The majority of patients received radiotherapy; only 4.4% received surgery only for early stages of the disease. Out of 158 patients receiving surgery, the majority (n = 143; 70.8%) received radical hysterectomy, six received simple hysterectomy, and nine surgeries were of unknown extent. Palliative radiotherapy was administered to almost half of the patients. Because of the lack of finances or availability of the drugs, only 96 patients received simultaneous radiochemotherapy (Table 2).

Survival

Within the whole cohort, a total of 212 deaths were registered. Another 37 patients were reported dead at the time of telephone interview, but the date of death remained unknown. Therefore, these patients were entered as alive and censored at the time of last personal appointment documented in the files. A total of 378 patients were lost to follow-up; therefore a worst-case analysis was performed (see Materials and Methods). The estimated overall survival is shown for the total patient cohort. The estimated 1- and 2-year survival probabilities were 90.4% and 73.6%, respectively (note at the end of year 3, the number of patients under observation declined to 8). In the worst-case analysis the estimated 2-year overall survival declined to 45.40% (Fig. 3). The median survival time was 40.6 months, declining to 21.5 months for the worst-case analysis. The estimated 2-year overall survival was most favorable for patients with FIGO stage Ia–IIa disease at the time of first presentation (84.8%, or worst-case 66.7%). Patients with FIGO stage IIb–IIIa had lower overall survival probabilities (79.5%, or worst-case 53.1%), and patients with FIGO stage IIIb–IVa the lowest (55.8%, or worst-case 25.3%) estimated

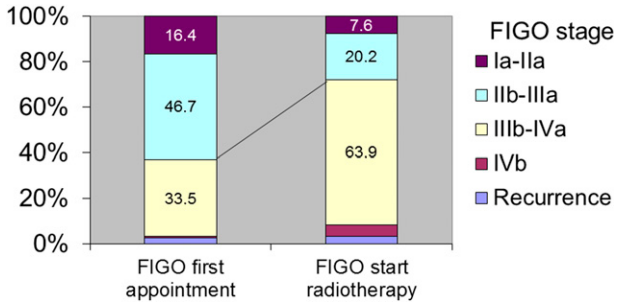


Figure 2. Changes in FIGO stage during waiting time. FIGO stage was evaluated at the first visit to the radiation oncologist at the Radiotherapy Department and then at the start of radiotherapy. The proportion of higher FIGO stages in the cohort increased during this period.

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

overall survival probabilities after 2 years. There were only a few patients with FIGO stage IVb disease ($n = 7$). Twenty-eight patients experienced recurrence. These cases together had an estimated 2-year overall survival probability of 54.6%, or worst-case 32.7%. Those patients represent a heterogeneous group with a rather unfavorable estimated survival probability (Fig. 4). Comparison of the FIGO stages showed relevant differences in survival probability between stages ($p < .001$). Comparing patients' outcome according to the dose of radiation showed better outcome for higher doses: 2-year survival probabilities were 80.8%, 72.3%, and 46.6% for 52 Gy and above, 32–50 Gy, and 4–30 Gy, respectively (supplemental online Fig. 2). Outcome by 2-year survival probabilities according to intention of treatment was best in the post-operative adjuvant situation (90.6%), radical radiotherapy (79.9%), followed by palliative radiotherapy (68.6%), and single fraction approach (50.3%) (Fig. 5).

Discussion

This is the first study from Ethiopia and also sub-Saharan Africa to report on the outcome of a large cohort of patients who received oncologic therapy for cancer of the cervix uteri. With a median follow-up time of 16.5 months (for surviving patients), the overall survival was 90.4% and 73.6% at 1 and 2 years, respectively. In total, 55.8% and 34.6% of the patients presented with stages IIb–IIIa and stage IIIb, respectively. We found extremely long waiting times until the start of radiotherapy (median 3.8 months) leading to even higher proportions of patients with late-stage disease by the time radiotherapy was started.

Cancer survival data from Africa are mainly based on cohorts from national or regional population-based registries. Therefore, we discuss our data with respect to these published results. It should be noted that the registry cohorts aim at including all cases irrespective of stage of disease or whether treatment was received. Our cohort lacks late-stage patients who died before the start of therapy and poor patients unable to pay for therapy ($n = 900$; Fig. 1). Therefore, because of the nature of our cohort, survival was expected to be more favorable compared with population-based data.

Table 2. Treatment modalities

Characteristics ($N = 1,059$ patients)	Number	Proportion (%)
Surgery only	47	4.4
Surgery and radiotherapy	111	10.4
Radiotherapy only	901	85.1
Radiotherapy	1,012	
Curative (60–72 Gy)	278	27.5
Palliative (44–50 Gy or hemostatic)	459	45.3
Palliative single fraction (10–38 Gy)	275	27.2
Chemotherapy		
Neoadjuvant to surgery (no radiotherapy)	2	0.2
Neoadjuvant to surgery followed by radiotherapy	26	2.4
Concurrent to curative radiotherapy	97	9.1
Palliative chemotherapy after palliative radiotherapy	54	5.1
For other neoplasia	2	0.2
No chemotherapy	878	82.9

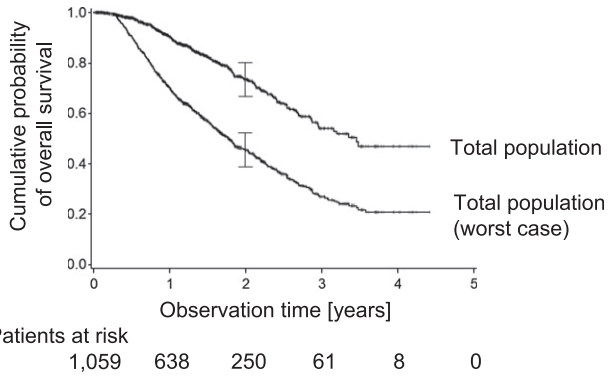
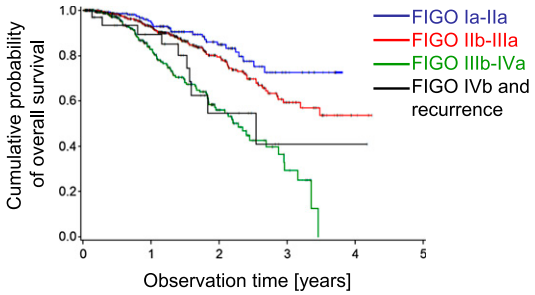


Figure 3. Cumulative overall survival probability. The uncorrected estimated overall survival time of the total cohort is shown (upper curve). The worst-case scenario assumes that patients who did not come to appointments for more than 6 months had died after the last appointment (lower curve).

Data from the population-based cancer registry of Kampala/Uganda show a 5-year age-standardized survival of 19% in 1993–1997 [19]. The Harare/Zimbabwe cancer registry ($n = 284$, half treated with radiotherapy) found a 3-year overall survival of 44.2% [20]. Sankaranarayanan et al. [21] report 5-year overall survival rates of 22% and 13% in the Gambia and Uganda, respectively. In our study, we found a 2-year overall survival of 74%, which is higher than the data from Zimbabwe and considerably better than the data from the Gambia and Uganda. This higher survival may point to a positive radiotherapy treatment effect beyond the lack of late-stage patients in our cohort.

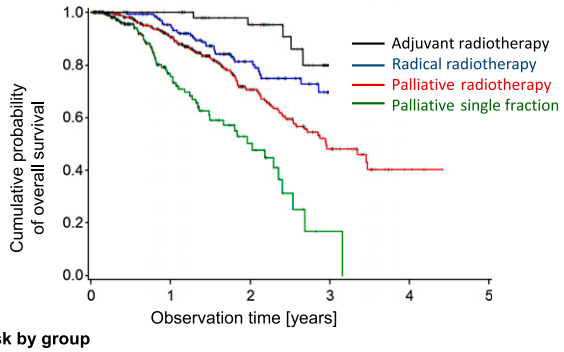
Looking at high-income countries, Petereit et al. [22] reviewed treatment results in 5,619 patients receiving external beam radiotherapy followed by high-dose brachytherapy as reported in original publications between 1985 and 1997. The FIGO stages in their cohort were comparable to our cohort. The



Patients at risk					
FIGO Ia-IIa	175	129	65	16	3
FIGO IIb-IIIa	494	347	134	36	4
FIGO IIIb-IVa	355	141	44	8	0
FIGO IVb+rec.	35	21	7	1	1

Figure 4. The estimated cumulative overall survival time according to FIGO stage at the first presentation to the radiation oncologist is shown. Group 1 is FIGO stage Ia–IIa, group 2 is FIGO stage IIb–IIIa, group 3 is FIGO stage IIIb–IVa, and group 4 is FIGO stage IVb and recurrences.

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; rec., recurrences.



n at risk by group					
Adjuvant RT	66	58	33	8	1
Radical RT	212	170	69	17	3
Palliative RT	459	303	104	34	4
Single fraction	275	58	16	0	0

Figure 5. The estimated cumulative overall survival time according to intent of radiation is shown.

Abbreviation: RT, radiotherapy.

overall 5-year survival probabilities were higher than our findings: 85%, 68%, and 47% for FIGO stages I, II, and III, respectively [22]. The lack of brachytherapy in our cohort may explain the lower survival probabilities observed.

Looking at medium income countries, overall 5-year survival probabilities from Asia and Central America (population-based registries, tumor stages unknown) were higher than our cohort: for example, China 82%, India, 46% and Costa Rica, 53% [21]. The African American population from the SEER database showed an overall 5-year survival of 58% [23]. The lack of early detection activities, as well as the lack of therapeutic options in our cohort, may explain the lower survival probabilities we observed.

Late stage at presentation is a major prognostic factor for decreased survival. In our cohort, 34.2% of the patients were diagnosed at FIGO stage IIIb and above. This is comparable with data reported from Cape Town/South Africa, where screening was not available between 1984 and 2000 [24]. As an example of a country with high screening activity, data from Germany showed that 66% and 22% of the women presented with T1 and T2 tumors, respectively [25]. Because of the lack of screening opportunities in Ethiopia, patients usually present late with symptomatic disease.

Prevention, screening, and early detection have been proven useful also in low-resource settings. In Africa, screening with visual inspection and acetic acid combined with immediate cryotherapy of suspicious lesions has been implemented regionally. Recently, the role of human papillomavirus (HPV) testing in screening programs is under discussion. Additionally, HPV vaccination has become a possible option for primary prevention [26–29]. In Ethiopia, there is little awareness of HPV and CC within society, and symptoms of vaginal bleeding are socially stigmatized. The benefits of modern therapy are still perceived as low [30]. Vaccination, screening, or early detection are not available for most of the population [15]. Studies from different African countries (e.g., Nigeria and Uganda) show positive uptake of screening service after community-based advocacy [31, 32]. Rwanda has now become the first country in Africa to implement a nationwide program, including vaccination, early detection, and screening [33]. These options could eventually change the burden of cervical cancer disease in Africa [4, 34].

As expected, we found a high proportion of HIV-positive patients (9.4%). The true rate may have been even higher, because general screening of all new patients was conducted only in years 2–4 of the study. The Ethiopia Demographic and Health Survey from 2010 reported that 1.5% of women aged 15–49 were HIV-positive [14]. Ongoing efforts in Ethiopia to screen HIV-positive women for cervical cancer seem justified [15].

There are certain factors that limit our results. First, there is no clinical information on patients who registered but never saw a physician (estimated $n = 463$). Economic reasons, logistic reasons, and progression of the disease are possible explanations. Other patients (estimated $n = 437$) saw a physician but never started therapy—the relevant files could not be retrieved. We assume that a number of very advanced cases were not included in this study, leading to more favorable characteristics than in the overall cohort of patients presenting at the referral hospital. Second, radiotherapy did not include the application of brachytherapy. This is known to be a suboptimal standard of treatment. Because half of all radiotherapy departments in Africa are not able to offer brachytherapy, we still consider these findings of interest for countries with limited resources. Third, we were unable to retrieve almost 400 files (27%) belonging to patients who received therapy. The files are handwritten and manually stored, and names also vary in spelling. Misplacing is common. We are not aware of any other reason for missing files, and therefore we do not suspect any associated selection bias. Despite these limitations, our study is the first to thoroughly characterize and follow >1,000 patients in the clinical setting and therefore adds information about cervical cancer in Africa to the literature.

Conclusion

In this study, we present a description and follow-up of 1,059 patients diagnosed with cancer of the cervix uteri between September 2008 and 2012 at Addis Ababa Radiotherapy Center. We found a relatively high estimated 2-year overall survival of

73.6% (declining to 45.5% in the worst-case analysis). This survival is higher than previously reported from African cancer registries. It probably reflects a positive effect of the treatment, as well as selection bias through lack of untreated late-stage patients in our hospital cohort. The survival is lower than that of treated patients in high-income settings, which probably reflects the lack of brachytherapy in Addis Ababa. Stage at presentation in Addis Ababa is late, and the disease progresses during waiting times. Later stages showed lower survival probabilities compared with earlier stages, and higher radiation doses showed higher survival probabilities compared with lower doses. There is an urgent need for increased awareness, primary prevention by vaccination, and early detection programs to increase early stages at presentation. To further improve survival, radiotherapy, including brachytherapy, should be made available sooner.

Acknowledgments

This work was done at Addis Ababa University. We thank the staff of Tikur Anbessa University Radiotherapy Center, who treated all of the cervical cancer patients. We also thank the nursing staff for obtaining the follow-up data and the record keeping staff for collecting the patient files.

Author Contributions

Conception/Design: Eva Johanna Kantelhardt, Ulrike Moelle, Matthias Begoihn, Adamu Addissie, Andreas Stang, Christoph Thomssen, Dirk Vordermark, Yirgu Gebrehiwot, Abreha Aynalem, Assefa Mathewos

Provision of study material or patients: Bekuretsion Yonas, Petros Hezkiel, Tufa Gemechu, Yirgu Gebrehiwot, Tigeneh Wondemagegnehu, Abreha Aynalem, Assefa Mathewos

Collection and/or assembly of data: Eva Johanna Kantelhardt, Ulrike Moelle, Matthias Begoihn, Adamu Addissie, Bekuretsion Yonas, Petros Hezkiel, Tufa Gemechu, Tigeneh Wondemagegnehu, Abreha Aynalem, Assefa Mathewos

Data analysis and interpretation: Eva Johanna Kantelhardt, Ulrike Moelle, Matthias Begoihn, Adamu Addissie, Pietro Trocchi, Bekuretsion Yonas, Petros Hezkiel, Andreas Stang, Christoph Thomssen, Dirk Vordermark, Tufa Gemechu, Yirgu Gebrehiwot, Tigeneh Wondemagegnehu, Abreha Aynalem, Assefa Mathewos

Manuscript writing: Eva Johanna Kantelhardt, Ulrike Moelle, Matthias Begoihn, Pietro Trocchi, Andreas Stang, Christoph Thomssen, Yirgu Gebrehiwot, Assefa Mathewos

Final approval of manuscript: Eva Johanna Kantelhardt, Ulrike Moelle, Matthias Begoihn, Adamu Addissie, Pietro Trocchi, Bekuretsion Yonas, Petros Hezkiel, Andreas Stang, Christoph Thomssen, Dirk Vordermark, Tufa Gemechu, Yirgu Gebrehiwot, Tigeneh Wondemagegnehu, Abreha Aynalem, Assefa Mathewos

Disclosures

Dirk Vordermark: Roche, Bristol-Myers Squibb, Lilly, Astra Zeneca (H). The other authors indicated no financial relationships.

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

References

1. Forouzanfar MH, Foreman KJ, Delossantos AM et al. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. Lancet 2011;378:1461–1484.

2. Cancer Incidence and Mortality Worldwide. International Agency for Research on Cancer. Available at: http://globocan.iarc.fr. Accessed March 30, 2014.

3. Bray F, Jemal A, Grey N et al. Global cancer transitions according to the Human Development Index (2008–2030): A population-based study. Lancet Oncol 2012;13:790–801.

4. Jemal A, Bray F, Forman D et al. Cancer burden in Africa and opportunities for prevention. Cancer 2012;118:4372–4384.

5. Bray F, Ren JS, Masuyer E et al. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer 2013;132:1133–1145.

6. Cancer in Africa: Epidemiology and Prevention. Parkin DM, Ferlay M, Hamdi-Cherif M, Sitas F, Thomas J, Wabinga H, Whelan SL, eds. IARC Scientific Publications No. 153. IARC Press Lyon, France 2003.

7. Abdel-Wahab M, Bourque JM, Pynda Y et al. Status of radiotherapy resources in Africa: An International Atomic Energy Agency analysis. Lancet Oncol 2013;14:e168–e175.

8. Parkin DM, Sitas F, Chirenje M et al. Part I: Cancer in indigenous Africans: Burden, distribution, and trends. Lancet Oncol 2008;9:683–692.

9. Curado MP, Edwards B, Shin HR et al. Cancer Incidence in Five Continents, Vol. IX: IARC Scientific Publications No. 160. Lyon, France: International Agency for Research on Cancer, 2009.

10. Dey S, Hablas A, Seifeldin IA et al. Urban-rural differences of gynaecological malignancies in Egypt (1999–2002). BJOG 2010;117:348–355.

11. Sighoko D, Bah E, Haukka J et al. Population-based breast (female) and cervix cancer rates in the Gambia: Evidence of ethnicity-related variations. Int J Cancer 2010;127:2248–2256.

12. Braun G, Fuhrer A, Breitenstein E et al. Cancer in Africa: AORTIC 8th International Cancer Conference 'Entering the 21st Century for Cancer Control in Africa' 30.11.-2.12.2011. Breast Care (Basel) 2012;7:177–179.

13. United Nations Population Estimates, "Total Population - Female." Available at http://esa.un.org/unpd/wpp/Excel-Data/population.htm. Accessed March 6, 2013.

14. Central Statistical Agency [Ethiopia] and ICF International. Ethiopia Demographic and Health-Survey 2011. 2012. Addis Ababa, Ethiopia and Calverton, Maryland, USA: Central Statistical Agency and ICF International.

15. Population Fact sheets Ethiopia. Available at http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. Accessed May 15, 2014.

16. Holmes MD, Dalal S, Volmink J et al. Non-communicable diseases in sub-Saharan Africa: The case for cohort studies. PLoS Med 2010;7:e1000244.

17. Olsen J, Bertollini R, Victora C et al. Global response to non-communicable diseases: The role of epidemiologists. Int J Epidemiol 2012;41:1219–1220.

18. Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. Int J Gynaecol Obstet 2009;105:107–108.

19. Wabinga H, Parkin DM, Nambooze S et al. Cancer survival in Kampala, Uganda, 1993–1997. IARC Sci Publ 2011;:243–247.

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

21. Sankaranarayanan R, Swaminathan R, Brenner H et al. Cancer survival in Africa, Asia, and Central America: A population-based study. Lancet Oncol 2010;11:165–173.

22. Petereit DG, Pearcey R. Literature analysis of high dose rate brachytherapy fractionation schedules in the treatment of cervical cancer: Is there an optimal fractionation schedule? Int J Radiat Oncol Biol Phys 1999;43:359–366.

23. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10–29.

24. Denny L, Anorlu R. Cervical cancer in Africa. Cancer Epidemiol Biomarkers Prev 2012;21:1434–1438.

25. Robert Koch-Institut (Hrsg) und die Gesellschaft der Epidemiologischen Krebsregister in Deutschland e.V. (Hrsg). Krebs in Deutschland 2007/2008: 8. Ausgabe. Berlin, Germany: Agentur Consalis-Media, 2012.

26. Denny L. Cervical cancer prevention: New opportunities for primary and secondary prevention in the 21st century. Int J Gynaecol Obstet 2012;119 (suppl 1):S80–S84.

27. Denny L, Kuhn L, Hu CC et al. Human papillomavirus-based cervical cancer prevention: Long-term results of a randomized screening trial. J Natl Cancer Inst 2010;102:1557–1567.

28. Sankaranarayanan R, Nene BM, Shastri SS et al. HPV screening for cervical cancer in rural India. N Engl J Med 2009;360:1385–1394.

29. Qiao YL, Sellors JW, Eder PS et al. A new HPV-DNA test for cervical-cancer screening in developing regions: A cross-sectional study of clinical accuracy in rural China. Lancet Oncol 2008;9:929–936.

30. Birhanu Z, Abdissa A, Belachew T et al. Health seeking behavior for cervical cancer in Ethiopia: A qualitative study. Int J Equity Health 2012;11:83–91.

31. Chigbu CO, Onyebuchi AK, Ajah LO et al. Motivations and preferences of rural Nigerian women undergoing cervical cancer screening via

visual inspection with acetic acid. Int J Gynaecol Obstet 2013;120:262–265.

32. Businge P, Nakimuli A, Nabunya E et al. Acceptability of cervical cancer screening via visual inspection with acetic acid or Lugol's iodine at Mulago Hospital, Uganda. Int J Gynaecol Obstet 2012;119:262–265.

33. Binagwaho A, Ngabo F, Wagner CM et al. Integration of comprehensive women's health programmes into health systems: Cervical cancer prevention, care and control in Rwanda. Bull World Health Organ 2013;91:697–703.

34. Arbyn M, de Sanjosé S, Saraiya M et al. EUROGIN 2011 roadmap on prevention and treatment of HPV-related disease. Int J Cancer 2012;131:1969–1982.

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

For Further Reading:

Julie S. Townsend, Analía Romina Stormo, Katherine B. Roland et al. Current Cervical Cancer Screening Knowledge, Awareness, and Practices Among U.S. Affiliated Pacific Island Providers: Opportunities and Challenges. ***The Oncologist*** 2014; 19:383–393.

Implications for Practice:

The U.S. Affiliated Pacific Island Jurisdictions (USAPIJ) are located in a geographically disparate region with a high burden of cervical cancer. Although cervical cancer screening providers in the USAPIJ stated that screening is a priority in clinical practice, costs associated with screening and varying levels of support for alternative screening tests pose barriers to screening throughout the USAPIJ. Use of alternative screening tests and routine monitoring and quality assurance to ensure all eligible women are reached may be needed to reduce the cervical cancer burden in the USAPIJ and to ensure effective use of limited resources.

Gizaw et al. Infectious Agents and Cancer (2017) 12:61
DOI 10.1186/s13027-017-0171-4

Infectious Agents and Cancer

RESEARCH ARTICLE Open Access

Cervical cancer patients presentation and survival in the only oncology referral hospital, Ethiopia: a retrospective cohort study

Muluken Gizaw[1,2*], Adamu Addissie[2], Sefonias Getachew[1,2], Wondimu Ayele[1,2], Israel Mitiku[4], Ulrike Moelle[5], Tigist Yusuf[2], Mathias Begoihn[5], Mathewos Assefa[6], Ahmedin Jemal[3] and Eva Johanna Kantelhardt[1,5]

Abstract

Background: Women infected with Human Immune Deficiency Virus (HIV) are assumed to be at higher risk of developing Cervical Cancer (CC). This is due to a rapid progression of pre-invasive to invasive lesions. However, evidences suggest, due to the availability of antiretroviral therapy (ART) and care services; an improved survival and treatment outcome of CC patients (CCPs) with HIV infection is expected.

Objective: The aim of this study is to examine the clinical characteristics and survival of of CCPs registered at the radiotherapy center of Tikur Anbessa Specialized Hospital (TASH), Addis Ababa University, Ethiopia.

Methods: We conducted a retrospective cohort study. Data from 1655 CCPs diagnosed between September 2008 and September 2012 were included. The primary endpoint was death from any cause. Kaplan-Meier estimates were compared using the log-rank test. Cox proportional hazards regression model was used to identify predictors of death. Data were analyzed using STATA version IC/14.

Results: The mean age of all patients was 49 years (SD = 11.6 years). Of all CCPs, 139 (8.4%) were HIV positive, 372 (22.5%) patients had a known negative HIV status and 1144 (69.1%) patients were asymptomatic with unknown HIV status. Due to late stage and waiting times, only 13.5% of the patients received curative radiotherapy doses. HIV-positive CCPs presented more often with advanced disease compared to HIV negative CCPs ((44.6%) versus 39.7%, $p = 0.007$). There was no significant difference in survival between HIV-positive and HIV-negative CCPs. Older age (HR = 2.01; 95% CI, 1.01,-4.05), advanced disease (HR = 2.6; 95% CI, 1.67–4.04) and baseline anemia (HR = 1.65; 95% CI, 1.24, 2.20) were independent predictors for higher risk of death.

Conclusion: Survival rates of CCPs did not differ according to HIV status. The risk of death was higher for patients with older age, advanced disease and anemia. HIV patients should be screened for CC according to guidelines to avoid late presentation.

Keywords: Uterine cervical neoplasms, HIV, Survival, Africa, Ethiopia

* Correspondence: muluken.gizaw@yahoo.com
[1]Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University, Halle (Saale), Germany
[2]Department of Preventive Medicine, School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia
Full list of author information is available at the end of the article

Background

Cancer and other non-communicable diseases (NCDs) have become leading causes of disability and death in developing countries, including Ethiopia [1]. Cervical Cancer (CC) is a leading cause of cancer morbidity and mortality in women globally. In 2012, 528, 000 new cases and 270,000 deaths were estimated to have occurred worldwide, with the majority of these cases and deaths (90%) occurring in low- and middle-income countries [2]. In Ethiopia, CC is the second most commonly diagnosed cancer and the leading cause of cancer death in women, with about 8000 newly diagnosed cases and 4700 deaths every year [3]. Most CC patients in Ethiopia seek healthcare at an advanced stage, when the effectiveness of treatment is limited [4].

Women infected with HIV are presumed to be more likely to have high risk Human Papilloma Virus (HPV) and have at least a 10% higher risk of developing CC [5–8]. HIV-positive patients are reported to more likely present with advanced stages of CC. It has been shown that HIV changes the natural history of HPV infection, resulting in a rapid progression to invasive lesions, and are associated with adverse survival probabilities [9]. The overall HIV prevalence in adult population of Ethiopia was 1.18% in 2016 with highest prevalence in Addis Ababa and Gambela regions with 4.9 and 4% respectively [10].

However, in the current context, due to the availability of ART and care services, an improved survival and treatment outcome of cervical cancer patients with HIV infection is expected. There is no adequate information documenting this evidence in Ethiopia. Hence, we conducted a retrospective cohort study to assess the survival rate of cervical cancer patients according to HIV status. We reviewed 1655 charts of women with cervical cancer from Tikur Anbessa University Hospital in Addis Ababa, Ethiopia.

Methods

Study design and population

We conducted a retrospective cohort study among cervical cancer patients diagnosed at Tikur Anbessa (Black lion) Specialized Hospital (TASH) from September 2008 to September 2012. TASH is the national teaching and referral hospital with more than 800 beds and offers diagnosis and treatment for approximately 400,000 in-patients and out-patients a year. The hospital receives patients who are referred from across the country, as well as patients from Addis Ababa. The hospital is the only one with a radiotherapy facility in Ethiopia. Patients were treated with surgery in the early stages and according to locally adapted guidelines at the radiotherapy center. Brachytherapy was not available at the time. Patients also may have registered but there after not received any treatment. Demographic and clinical characteristics of the patients were retrieved from individual patient charts. The survival status of patients was collected from the cancer registry which obtained information from patient cards or via telephone calls,

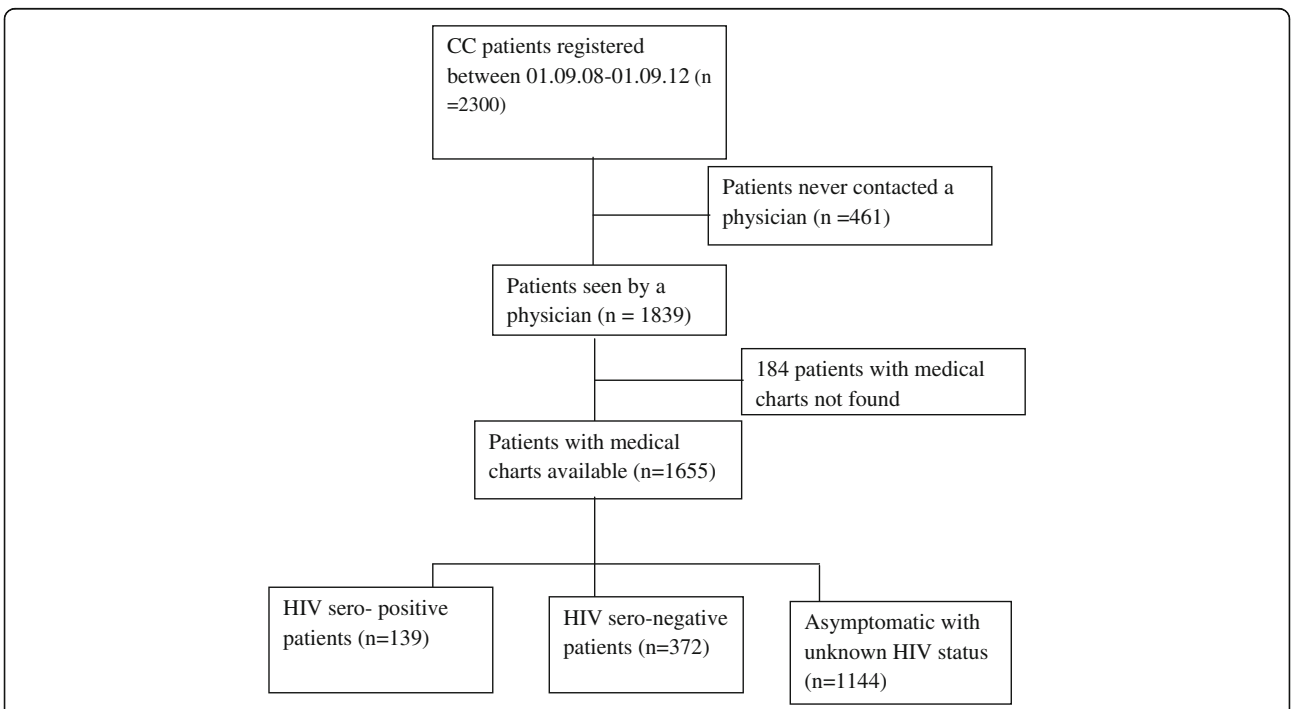


Fig. 1 Total number of cervical cancer Patients from radiotherapy center at TASH, Addis Ababa, Ethiopia, included in the final analysis (Strobe diagram)

Study variables and data collection

HIV status identification

The HIV status of each patient was retrieved from medical charts by trained medical staff. Only half of the patient's charts contained a registered HIV status. HIV status was documented if the patient had been screened for HIV. Since September 10, 2011 every patient registered at TASH had been screened for HIV on a regular basis. Before this, only patients with a high risk profile (e.g., HIV-positive partner) or clinically suspicious patients were screened. The HIV status was tested using the enzyme-linked immunosorbent assay method. We grouped HIV status into three categories: HIV-positive, HIV-negative and HIV unknown.

Study outcome and definition

The primary objective of this study was to compare the overall survival of CC patients according to HIV status. We estimated follow-up time between the date of first presentation and the last date of observation. The last date of observation was defined as either death or censoring at the last known alive.

Data analysis

STATA version IC/14 (StataCorp, College Station, TX, USA) was used for statistical analyses. The overall survival of HIV positive and negative patients was estimated using Kaplan-Meier methods. Kaplan-Meier estimates were compared using the log-rank test. Cox proportional hazards regression model was used to identify predictors for survival. Influences of prognostic factors were estimated using hazard ratios with 95% confidence intervals (CI).

Ethical considerations

Ethical approval was obtained from the institutional review board of the College of Health Sciences, Addis Ababa University and Martin Luther University, Halle Germany. The confidentiality of the patient status was maintained by avoiding personal identifiers during analysis.

Results

Of the 1839 cervical cancer patients registered and seen by physicians at TASH, medical charts were retrieved for 1655 (90.0%). Of the 1655 patients with a medical chart, 139 (8.4%) were HIV-positive, 372 (22.5%) were HIV-negative and 1144 (69.1%) were asymptomatic with unknown HIV status (see Fig. 1).

Of all patients, 1081(65.3%) patients received any form of radiotherapy, 190 (11.5%) underwent surgery and 206 (12.4%) received chemotherapy. Among patients treated by radiotherapy, non- radical radiotherapy was provided for 770 (71.0%) of stage IIIB and IVA patients. Of the 190 patients who underwent surgery, 155 (81%) received

Table 1 Demographic and clinical characteristic of cervical cancer patients according to HIV status, TASH, Addis Ababa, Ethiopia, 2008–2012

Patient demographic characteristics	HIV status		
	HIV negative n (%)	HIV positive n (%)	HIV unknown n (%)
Residence			
Urban	128 (34.4)	82 (59)	431 (37.7)
Rural	244 (65.6)	57 (41)	713 (62.3)
Marital status			
Single	3 (0.8)	5 (3.6)	4 (0.4)
Married	297 (79.8)	113 (81.3)	928 (81.1)
Unknown	72 (19.4)	21 (15.1)	212 (18.5)
Age category			
< 30	15 (4.0)	29 (20.9)	47 (4.1)
30–39	81 (21.8)	58 (41.7)	243 (21.2)
40–49	131 (35.2)	40 (28.8)	389 (34)
50–59	88 (23.7)	10 (7.2)	295 (25.8)
60+	57 (15.3)	2 (1.4)	170 (14.9)
FIGO stage at presentation			
I-IIA	59 (15.8)	10 (7.2)	95 (8.3)
IIB-IIIA	148 (39.8)	57 (41.0)	51 (45.1)
IIIB-IVA	144 (38.7)	62 (44.6)	458 (40.0)
IVB	6 (1.6)	5 (3.6)	15 (1.3)
Post-operative	7 (1.9)	2 (1.4)	23 (2.0)
Recurrence	7 (1.9)	3 (2.2)	28 (2.5)
Unknown	1 (0.3)	0	9 (0.8)
Anemia Status			
No anemia ≥12	186 (50)	51 (36.7)	437 (38.2)
> 10 and <12	93 (25)	38 (27.3)	373 (32.6)
8–10	36 (9.7)	24 (17.3)	153 (13.4)
> 5 and <8	24 (6.5)	12 (8.6)	73 (6.4)
< 5	15 (4.0)	12 (8.6)	60 (5.2)
Unknown	18 (4.9)	2 (1.4)	48(4.2)
Co-morbidity status			
No co morbidity	341 (91.7)	124 (89.2)	1045(91.3)
Any co morbidity	31 (8.3)	15 (10.8)	99 (8.7)
Treatment modalities			
Radiation	187 (63.8)	105 (79.5)	789 (75.0)
Surgery	71 (24.2)	12 (9.0)	107 (10.0)
Chemotherapy	35 (12.0)	15 (11.5)	156 (15.0)
Patient outcome			
Alive	331 (89.0)	108 (77.7)	930 (81.3)
Dead	41 (11.0)	31 (22.3)	214 (18.7)
Total	372	139	1144

radical hysterectomy and nine received a simple hysterectomy (see Table 1).

Patient characteristics

Table 1 shows the demographic and clinical characteristics of patients according to their HIV status. The mean age of all patients at entry was 49 years. The majority of cervical cancer patients with HIV-positive status came from urban areas (59%), while the majority of patients with HIV-negative, HIV unknown status were rural residents (62 and 66%, respectively). The majority of HIV-positive cervical cancer patients were between 30 and 39 years old (42%), with mean age of 39 (SD = 9) whereas HIV negative, HIV unknown cervical cancer patients were between 40 and 49 years (35 and 34%, with mean age of 50, respectively). About 81% of cervical cancer patients were married. The International Federation of Gynecology and Obstetrics (FIGO) stage at presentation for HIV-positive patients was IIB-IIIA (41%) and IIIB-IVA (44.6%); for HIV-negative/unknown patients IIB-IIIA (40 and 45%, respectively) and IIIB-IVA (39 and 40%, respectively). A total of 120(86.3%) of HIV positive women were on ART.

Survival according to HIV status

A total of 286 (17.3%) cervical cancer patients died during the follow-up period. The median survival time was 38 months.. Of the total deaths, 41(11%) and 31(22.3%) were HIV negative and HIV Positives. The median survival of HIV positives and HIV negative was 29 and 28 months respectively.

Crude survival probabilities did not differ between patients according to HIV status. After adjusting for place of residence, age, FIGO stage, co-morbidity (yes/no) and baseline anemia status, no difference in survival probability was seen between HIV-positive and HIV-negative/unknown cervical cancer patients (HR = 1.16, 95%CI 0.70–1.91) (see Fig. 2).

Survival according to other clinical and demographic characteristics

After adjusting for place of residence, HIV status, FIGO stage, co-morbidity and baseline anemia status, older CC patients had a two-fold higher risk of death than younger patients (HR = 2.02, 95%CI: 1.01–4.05). CC patients with higher cancer stage (FIGO IIB-IIIA and recurrence) had a higher risk of death, with HR = 2.60 (95%CI: 1.67–4.04) and HR = 2.77 (95%CI: 1.35–5.68), respectively, compared to those with a lower stage. Cervical cancer patients with anemia at baseline were more likely to die than non-anemic patients with HR = 1.65 (95%CI: 1.24–2.20) and HR = 1.84 (95%CI: 1.27–2.66) for a hemoglobin level of greater than 10 and between 8 and 10, respectively. Place of residence and co-morbidity status did not show any differences in overall survival of CC patients (see Table 2).

Discussion

This study showed that CC patients with known HIV infection constituted 8.4% of all CC patients registered in the largest referral hospital in Ethiopia. The survival rate was similar among CC patients with and without known HIV infection in this cohort where only 14% of patients received any form of therapy considering only the curative radiotherapy. The majority of patients with known HIV infection came from the urban area, compared to patients without HIV infection. About 86% of the HIV positive CCPs were on ART. A slightly higher proportion of patients with HIV infection presented with late-

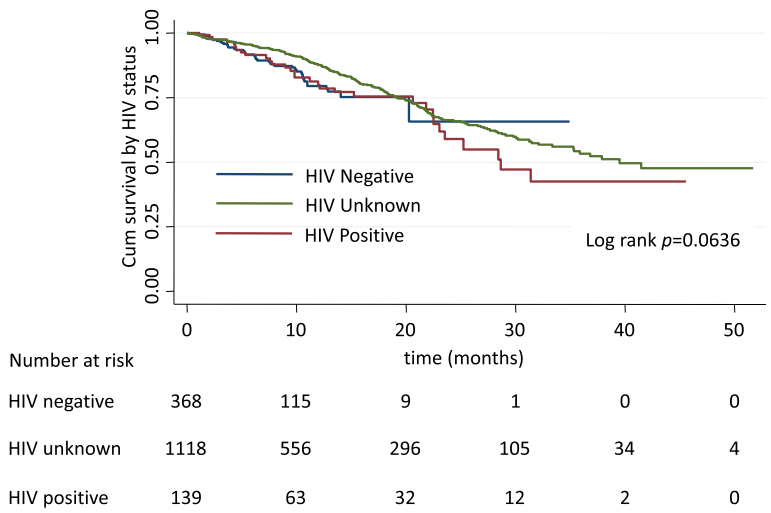


Fig. 2 Kaplan-Meier estimates of survival of cervical cancer patients according to HIV status among TASH patients, Addis Ababa, Ethiopia, 2008–2012

Table 2 Demographic and clinical characteristic associated with the survival of cervical cancer patients, TASH, Addis Ababa, Ethiopia, 2008–2012

Characteristics	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	*P*-value
HIV status			
Positive	1.00	1.00	
Negative	1.13(0.70,1.81)	1.16(0.70,1.91)	0.564
Unknown	0.77(0.53,1.13)	0.76(0.51,1.15)	0.206
Residence			
Rural	1.2(0.94,1.51)	1.16(0.91,1.48)	0.212
Urban	1.00	1.00	
Age group			
< 30	1.00	1.00	
30–39	1.52(0.78,2.97)	1.43(0.73,2.82)	0.290
40–49	1.50(0.78,2.86)	1.47(0.75,2.87)	0.259
50–59	1.12(0.57,2.20)	1.17(0.58,2.36)	0.650
60+	1.83(0.93,3.61)	2.01(1.01,4.05)[a]	**0.049**
FIGO stage at presentation			
I-IIA	1.00	1.00	
IIB-IIIA	1.32(0.86,2.03)	1.22(0.79,1.88)	0.372
IIIB-IVA	3.07(2.00,4.71)	2.60(1.67,4.04)[a]	**<0.001**
IVB	3.77(1.13,12.55)	2.54(0.74,8.68)	0.137
Post-operative	1.17(0.45,3.07)	1.04(0.40,2.74)	0.930
Recurrence	2.46(1.21,5.00)	2.77(1.35,5.68)[a]	**0.005**
Anemia: Hgb level at presentation (g/dl)			
No anemia ≥12	1.00	1.00	
> 10 and <12	1.82(1.38,2.40)	1.65(1.24,2.20)[a]	**0.001**
8–10	2.20(1.54,3.14)	1.84(1.27,2.66)[a]	**0.001**
< 8 and ≥5	1.47(0.90,2.42)	1.35(0.81,2.25)	0.242
< 5	1.24(0.67,2.31)	1.12(0.60,2.10)	0.706
Unknown	1.74(0.23,12.73)	1.21(0.16,8.96)	0.846
Co-morbidity status			
No co-morbidity	1.00	1.00	
Any co-morbidity	0.98(0.68,1.40)	0.99(0.68,1.43)	0.969

HR hazard ratio, *CI* confidence interval, *HIV* Human Immune deficiency Virus, *FIGO* International Federation of Gynecology and Obstetrics
values in boldface are statistically significant at alpha of 0.05

stage cancer. The median time of observation in patients without event was 38 months. Older age, late-stage disease and anemia were factors significantly influencing overall mortality probabilities of cervical cancer patients.

The survival of CC patients with positive HIV status was similar to those with negative or asymptomatic with unknown HIV status. The observed survival of HIV positive patients could have been compromised for two reasons: either because they die due to the HIV infection or second because the CC is more aggressive. Since we do not have information on cause of death in our study, we can only suggest that the widespread use of ART in this cohort may prevent HIV related deaths and also fast progression of CC [11–13].

A higher proportion of HIV-infected cervical cancer patients presented with advanced stages of cancer compared to those with negative/unknown HIV status. This is probably because the HIV infection decreases the progression time of cervical cancer to more advanced stages [9, 14].

In our Cox model, we found older age, baseline anemia and advanced stage to be significantly associated with higher all-cause mortality of cervical cancer patients. This finding is consistent with studies conducted

in similar settings elsewhere. According to a Nigerian study, there was a 41% higher proportion of death for advanced stages compared to early stages [15]. Moreover, a Kenyan finding showed that the 2-year survival of cervical cancer patients at advanced stage was less than 20% [16].

Baseline anemia independently predicted a higher risk of death; moderate anemia was significantly associated with higher mortality compared to patients with no anemia. In this study, anemia was defined as a hemoglobin level below 12 g/dl. Another similar study from north-central Nigeria indicated baseline anemia to be an independent predictor of lower survival in cervical cancer patients [15]. Furthermore, older (≥60 years) patients had a significantly higher risk of death compared to younger patients. Several other studies have also reported this [17, 18]; this might be due to fact that young patients are more likely to respond to treatment and present in an early stage [17]. In addition, it has to be considered that the probability for all-cause death is higher in the older age groups.

The strength of this study is the large number of all CC patients with medical charts available during a 4-year period in TASH, the only hospital for cancer treatment in Ethiopia and the inclusion of those patients who only registered but never received treatment were included. However, a limitation is the large proportion of CC patients with only asymptomatic with unknown HIV status. Since their characteristics were very similar to those with negative HIV sero-status we assume they are more likely to be HIV sero-negative. However, this may have underestimated the effect of HIV on the survival of CC patients. Moreover, about 20% of all cervical cancer patients who registered at TASH and were scheduled to see a physician for treatment planning during the study period did not come back; these patients may have had very advanced disease. We assume that the 10% of charts missing were random cases due to problems of misplacing, or miss-spelling names or numbers. The huge efforts that would have been needed to retrieve these charts were out of scale.

Conclusion

In conclusion, known HIV-positive patients constitute a considerable proportion of CC patients in a hospital cohort in Ethiopia and are diagnosed at a more advanced stage of disease compared to those with negative and unknown status. Survival did not differ between HIV-positive and HIV-negative and -unknown CC patients after adjusting for other prognostic factors. The high proportion of advanced stage cancer in HIV-positive patients suggests the need to increase the implementation and awareness of cervical cancer screening among HIV-positive women and remove barriers to accessing screening. Anemia at presentation probably reflects the severity of disease and therefore shows adverse survival. Attention should be given generally to those CC patients who are diagnosed at older age and with advanced stage of disease, as these are contributing factors for lower survival rates. Finally, a high proportion of unknown HIV status justifies screening for HIV in all CC patients, this is now in place.

Abbreviations

ART: Antiretroviral Therapy; CC: Cervical Cancer; CCPs: Cervical Cancer Patients; CI: Confidence Intervals; FIGO: International Federation of Gynecology and Obstetrics; HIV: Human Immune Deficiency Virus; HPV: Human Papilloma Virus; HR: Hazard Ratio; NCDs: Non-communicable Diseases; SD: Standard Devation; TASH: Tikur Anbessa Specialized Hospital

Acknowledgements

Authors would like to thank the staff members of Tikur Anbessa Specialized Hospital Radiotherapy Center who treated and provided care for all cervical cancer patients. We also grateful to Mrs. Tinsae and Mrs. Tigist for obtaining the follow-up data and Mrs. Mulu and Mr. Neme for collecting the patient files.

Funding

Funding for this research was provided by the Federal Ministry of Research and Education of Germany, grant number 01DG12006 and 01DG13026. This work was also supported by the German Ministry for Economic and Development Cooperation (BMZ) through the ESTHER University and Hospital Partnership Initiative of German International Cooperation (GIZ).

Availability of data and materials

- The datasets analyzed are available from the corresponding author on reasonable request.

Authors' contributions

MG performed statistical analysis and draft the manuscript. EK and AA participated in designing the study, analysis, reviewing and editing the final manuscript and contributed to the discussion. UM, TY and MB carried out the conception, designing the study and data collection. SG, WA, IM, MA and AJ have been involved in revising the manuscript critically with valid inputs. All authors read and approved the final form of the manuscript.

Ethics approval and consent to participate

Ethical approval was obtained from the institutional review board of the College of Health Sciences, Addis Ababa University and Martin Luther University, Halle Germany.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Author details

[1]Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University, Halle (Saale), Germany. [2]Department of Preventive Medicine, School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia. [3]Department of Intramural Research, American Cancer Society, Atlanta, GA, USA. [4]Department of Public Health, College of Medicine and Health Sciences, Wollo University, Dessie, Ethiopia. [5]Department of Gynecology, Martin-Luther-University, Halle (Saale), Germany. [6]Radiotherapy Center, School of Medicine, Addis Ababa University, Addis Ababa, Ethiopia.

Received: 21 September 2017 Accepted: 23 November 2017
Published online: 29 November 2017

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. Lancet (London, England). 2012;380(9859):2095–128.
2. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108.
3. ICO. Human Papilloma Virus and related cancers, fact sheet; 2016. Available from: URL: http://www.hpvcentre.net/statistics/reports/ETH_FS.pdf. Cited 14 July 2016.
4. Kantelhardt EJ, Moelle U, Begoihn M, et al. Cervical cancer in Ethiopia: survival of 1,059 patients who received oncologic therapy. Oncologist. 2014; 19(7):727–34.
5. Denslow SA, Rositch AF, Firnhaber C, et al. Incidence and progression of cervical lesions in women with HIV: a systematic global review. Int J STD AIDS. 2014;25(3):163–77.
6. WHO. Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention: 2013.
7. Vuyst H, Mugo NR, Chung MH, et al. Prevalence and determinants of human papillomavirus infection and cervical lesions in HIV-positive women in Kenya. Br J Cancer. 2012;107(9):1624–30.
8. Denny L, Boa R, Williamson AL, et al. Human papillomavirus infection and cervical disease in human immunodeficiency virus-1-infected women. Obstet Gynecol. 2008;111(6):1380–7.
9. Clarke B. Postmodern cancer: the role of human immunodeficiency virus in uterine cervical cancer. Mol Pathol. 2002;55(1):19–24.
10. The Ethiopian Public Health Institute (EPHI). HIV related estimates and projections for Ethiopia–2017; 2017. Available from: URL: https://www.ephi.gov.et/images/pictures/download2009/HIV_estimation_and_projection_for_Ethiopia_2017.pdf. Cited 15 Nov 2017.
11. Bonnet F, Burty C, Lewden C, et al. Changes in cancer mortality among HIV-infected patients: the mortalité 2005 survey. Clin Infect Dis. 2009;48(5):633–9.
12. Collaborative analysis of 13 HIV cohort studies. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996-2006. Clin Infect Dis. 2010;50(10):1387–96.
13. Gotti D, Raffetti E, Albini L, et al. Survival in HIV-infected patients after a cancer diagnosis in the cART Era: results of an Italian multicenter study. PLoS One. 2014;9(4):e94768.
14. Mbulaiteye SM, Bhatia K, Adebamowo C, et al. HIV and cancer in Africa: mutual collaboration between HIV and cancer programs may provide timely research and public health data. Infect Agent Cancer. 2011;6(1):16.
15. Musa J, Nankat J, Achenbach CJ, et al. Cervical cancer survival in a resource-limited setting-North Central Nigeria. Infect Agent Cancer. 2016;11:15.
16. Maranga IO, Hampson L, Oliver AW, et al. Analysis of factors contributing to the low survival of cervical cancer patients undergoing radiotherapy in Kenya. PLoS One. 2013;8(10):e78411.
17. Zhou J, Li X, Huang K, et al. Young cervical cancer patients may be more responsive than older patients to neoadjuvant chemotherapy followed by radical surgery. PLoS One. 2016;11(2):e0149534.
18. Dryden P, Scott B, Suneja G, et al. HIV infection and survival among women with cervical cancer. JCO. 2016;34(31):3749–57.

The Oncologist®

Global Health and Cancer

Cervical Cancer in Ethiopia: The Effect of Adherence to Radiotherapy on Survival

Ulrike Moelle,[a] Assefa Mathewos,[b] Abreha Aynalem,[b] Tigeneh Wondemagegnehu,[b] Bekuretsion Yonas,[b] Matthias Begoihn,[a] Adamu Addissie,[b] Susanne Unverzagt,[a] Ahmedin Jemal,[c] Christoph Thomssen,[a] Dirk Vordermark,[a] Eva J. Kantelhardt[a]

[a]Martin Luther University, Halle an der Saale, Germany; [b]Addis Ababa University, Addis Ababa, Ethiopia; [c]American Cancer Society, Atlanta, Georgia, USA

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

Key Words. Cervical cancer • Radiotherapy • Sub-Saharan Africa • Survival • Adherence

Abstract

Background. Discontinuation of radiotherapy (RT) for cervical cancer (CC) in sub-Saharan Africa is common because of patient- and health service-related reasons. This analysis describes toxicities and the effect of adherence on survival.

Materials and Methods. A total of 788 patients with CC (2008–2012) who received RT at Addis Ababa University Hospital were included. External beam RT without brachytherapy was performed according to local guidelines. We previously described survival and prognostic factors. Now we analyzed adherence and survival according to total doses received. Adjustment via multivariate cox regression analysis was done.

Results. One-year overall survival (OS) after radical RT ($n = 180$) for International Federation of Gynecology and Obstetrics (FIGO) stages IIA–IIIA was 89% for discontinuation (<72 Gy) and 96% for adherence (≥72 Gy; hazard ratio [HR], 1.3; 95% confidence interval [CI], 0.5–3.3). One-year OS after nonradical RT ($n = 389$) for FIGO stages IIIB–IVA was 71% for discontinuation (<40 Gy) and 87% for adherence (44–50 Gy; HR, 3.1; 95% CI, 1.4–6.9). One-year OS for FIGO stages IIIB–IVB ($n = 219$) after one compared with two or more palliative single fractions of 10 Gy were 14% and 73% respectively (HR, 7.3; 95% CI, 3.3–16). Reasons for discontinuation were toxicities, economic background, and RT machine breakdown. Grade 1–2 late toxicities were common (e.g., 30% proctitis, 22% incontinence). Grade 3 early and late toxicities were seen in 5% and 10% respectively; no grade 4 toxicities occurred.

Conclusion. Patients who adhered to guideline-conforming RT had optimum survival. Better supportive care, brachytherapy to reduce toxicities, socioeconomic support, and additional radiation capacities could contribute to better adherence and survival.

The Oncologist 2018;23:1024–1032

Implications for Practice: This study presents the effect of adherence on survival of 788 patients with cervical cancer receiving external beam radiotherapy without brachytherapy in Ethiopia. Discontinuation of planned radiotherapy according to local guidelines considerably reduced survival for all International Federation of Gynecology and Obstetrics (FIGO) stages treated (hazard ratios were 1.3, 3.1, and 7.3 for FIGO stages IIA–IIIA and IIIB–IVA and the palliative approach, respectively). Early toxicity (5% grade 3) should be treated to improve adherence. Economic difficulties and machine breakdown should also be addressed to reduce discontinuation and improve survival.

Introduction

Cancer of the uterine cervix (CC) is the leading cause of cancer death among women in sub-Saharan Africa [1] and other parts of the economically developing world, largely because of limited access to early detection and treatment services [2]. CC tragically serves as a symbol for global health disparity. The age-standardized death rate per 100,000 women in east Africa is 12 times as high as in western Europe (25.3% vs. 2%) [3].

Patients with CC diagnosed with early stage disease (stage IIA or lower) are primarily treated with surgery, whereas those patients diagnosed with advanced stage disease (stage IIB or higher) are treated with chemoradiation [4]. Because of the lack of early detection services, most patients with CC in sub-Saharan Africa are diagnosed at a late stage of the disease [5, 6], and thus they are candidates for radiotherapy (RT). However, the availability of RT services is limited in this part of the world. In Africa, 28 countries lack any RT facility [7]. Even in those countries with RT, the number of RT machines is woefully inadequate. Furthermore, 30% of RT machines in Africa are Cobalt-60 units rather than intensity-modulated RT using linear accelerators (LINACs), which are the standard of care because they reduce

Correspondence: Eva J. Kantelhardt, M.D., Department of Gynaecology, Institute of Medical Epidemiology, Biostatistics and Informatics, Martin Luther University, Ernst-Grube-Str. 40, 06120 Halle (Saale), Germany Telephone: 49-345-557-1847; e-mail: eva.kantelhardt@ukhalle.de Received June 8, 2017; accepted for publication February 14, 2018; published Online First on March 23, 2018. http://dx.doi.org/10.1634/theoncologist.2017-0271

adverse effects from unnecessary irradiation of surrounding tissues [8]. However, Cobalt-60 units with more superficial and less sharp beam penetration are cheaper to install and maintain, easier to operate, much less dependent on reliable electrical power, and less vulnerable to changes in humidity or temperature [9]. Regardless of the type of RT, the combination of external beam RT (EBRT) with intracavitary brachytherapy (ICBT) is strongly better re-commended for International Federation of Gynecology and Obstetrics (FIGO) stages IIB–IVA [4]. In these cases, the tumor center should receive a total radiation dose of 80–95 gray (Gy) [4]. Despite the importance of ICBT in the treatment of CC, in 2010 brachytherapy services were available in merely 20 of 52 African countries, Ethiopia not among them [10].

Ethiopia is the second most populated African country, preceded by Nigeria, with over 44 million women and girls [11]. According to GLOBOCAN 2012 estimates, 7,095 women are newly diagnosed with CC every year in Ethiopia [12]. Access to adequate treatment for these women is severely limited, as only one RT machine exists in the country, hosted by the Radiotherapy Center of Tikur Anbessa University Hospital (TAHRC). The staff of the center comprises the only four radiation oncologists in the whole country. Until the closing date of this study (August 7, 2013), RT at TAHRC was performed solely as EBRT by a Theratron Equinox 80 Cobalt-60 unit (Best Theratronics Ltd., Ottawa, Canada) with a source-to-surface distance of 80 cm without additional ICBT. The Cobalt-60 unit is in daily use from 8 AM to 5 PM and is subject to monthly maintenance procedures during which no patients are treated. In 2014, we reported long waiting times for patients treated in the years 2008 to 2012, which resulted in a considerable stage migration. Data on patient baseline characteristics, waiting times, and overall survival have been previously published [13]. However, regarding RT guidelines for patients with CC in Ethiopia, there are no published data on adherence and outcome. In order to guarantee reliable health care standards, treatment guidelines need to be transparent and comparable throughout centers [14]. In terms of oncological RT, underdosing, resulting in residual disease or recurrence, might be as harmful as overdosing. Radiation toxicities or secondary cancers similarly lead to decreased quality of life and even lower survival.

The primary purpose of this study is to assess the current practice of RT for CC at TAHRC by means of a dose-specific survival analysis. The outcomes of patients who adhered to guideline-conforming RT were compared with those of patients who discontinued RT in order to draw conclusions about whether and to what extent patients benefit from adherence to guideline-conforming RT.

Materials and Methods

Patients and Methods

All women with histologically verified cancer of the cervix uteri (International Classification of Diseases for Oncology codes C53.0–9) who were diagnosed and treated with RT between September 11, 2008, and September 11, 2012, at TAHRC, were screened for inclusion to the study. Patients whose cervix uteri was surgically removed, patients who did not receive RT to the pelvis, and patients who were not assigned to RT according to TAHRC guidelines were excluded. All patient and tumor characteristics, diagnostic results, and therapy information were extracted from patients' files. Regarding data on human immunodeficiency virus (HIV) status, regular screening started in the third year of data collection on September 10, 2011. If several analgesics were used, only the most potent analgesic was documented.

Patients were followed up every 6 months after the end of RT at TAHRC. For information on survival, adverse effects, and state of disease, the files' last date of personal contact and additional information from patients or their relatives via phone calls were used. For differentiation of acute and late adverse effects, data collected within the first 3 months after the last day of RT were documented separately from those collected afterwards. The Common Terminology Criteria for Adverse Events, version 4.0 [15] were applied for grading the toxicities.

Staging

Tumors were classified according to the FIGO staging system [16] by at least one of the four radiation oncologists at TAHRC. In cases of discrepancy between two physicians, another radiation oncologist was consulted. An additional radiologic or sonographic suspicion of distant metastasis or hydronephrosis resulted in upstaging at the time of RT planning. Histological results were documented according to pathology reports.

Radiotherapy

Indications for RT were stages of FIGO higher than IIA or lower stages for inoperable patients. Renal failure and FIGO stage IVB were contraindications to curative RT. Planning of RT consisted of reassessment of FIGO stage and marking the optimal beam entry 3 cm cranially from the pubis with an intradermal ink injection. Body imaging was not available. For calculation of tumor-to-skin distance for anterior-posterior field and lateral field size, the sagittal and transversal diameters at the marked localization were measured and bisected.

RT was performed either curatively as radical and nonradical RT or as palliation with monthly single fractions (Fig. 1). For details, see Kantelhardt et al. [13]. Radical and nonradical RT were applied in two phases. Patients with FIGO stage IIB–IIIA were planned to receive a total dose of 72 Gy (radical RT), which were distributed in 23 fractions at 2 Gy each within 5 to 6 weeks in the first phase and 13 fractions at 2 Gy each within 2 to 4 weeks in the second phase. Patients with FIGO stage IIIB or IVA without bilateral hydronephrosis or vesicovaginal fistula received a nonradical RT pattern with a total dose of 44–50 Gy and larger doses per fraction: 8 fractions of 4 Gy within 4 weeks in the first phase, followed by a second phase of 12 or 18 Gy (4 or 6 fractions of 3 Gy each) within 2 to 3 weeks. Patients with FIGO stage IVA or IIIB with bilateral hydronephrosis, IVA with clinical fistula, or IVB received palliative RT: monthly single fractions of 10 Gy each with a maximum 28 Gy in total, with a third single fraction of 8 Gy.

Statistical Analysis

The primary endpoint of this study was overall survival. Person time equaled the time from the first day of RT to death, censoring, or closing date (August 7, 2013), whichever came first. Probabilities of overall survival were estimated using the Kaplan-Meier method. The 95% confidence intervals (95% CIs) at years one and two were shown. The Cox proportional

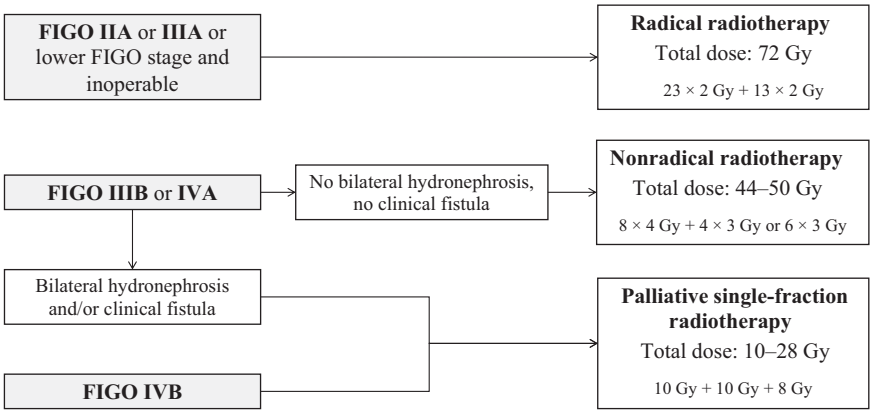


Figure 1. Criteria for therapeutic decision making at the Radiotherapy Center of Tikur Anbessa Hospital, Addis Ababa, Ethiopia. Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

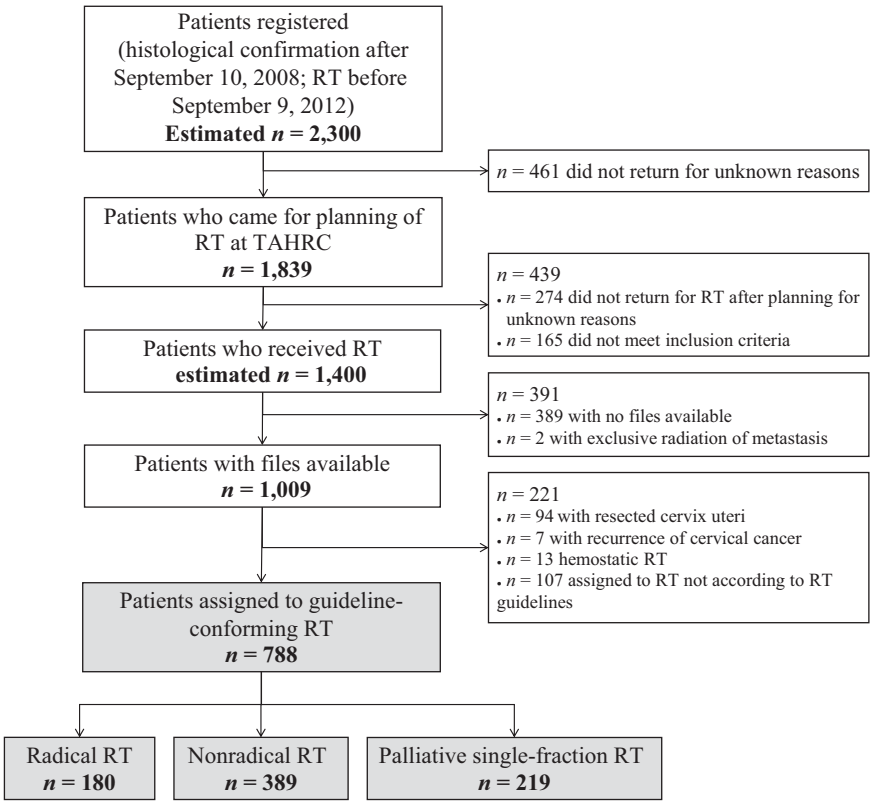


Figure 2. CONSORT diagram for study at Tikur Anbessa Hospital Radiotherapy Center. Abbreviations: RT, radiotherapy; TAHRC, Tikur Anbessa Hospital Radiotherapy Center.

hazards model [17] was used to describe differences between patients who discontinued and those who adhered. Confounders were identified by directed acyclic graphs: grade of anemia, the respective RT schedule, performance status, estimated glomerular filtration rate and HIV status. Analyses were conducted using SPSS Statistics, version 24 (IBM, Armonk, NY). The median follow-up time for patients was 9.6 months. Right censoring was assumed to be unrelated to the risk of death. As most (81%) of the 788 patients were censored, an additional worst-case analysis based on the follow-up intervals of 6 months was performed: all patients who were neither seen nor reached by telephone calls within 6 months after last contact were assumed to have died 1 day after last contact.

Ethics

Ethical approval was obtained from the Addis Ababa University of Health Science and the Medical Faculty of Martin-Luther University Halle-Wittenberg. The study was conducted without individual informed consent, as the study relied on retrospective data collected as part of routine patient care. For follow-up interviews by telephone, patients or relatives gave oral consent.

Results

Description of the Study Population

As displayed in Figure 2, an estimated 1,009 patients at TAHRC had treatment records available. Out of those, 788

Table 1. Basic demographic and disease-specific data of all 788 patients

Characteristics	*n* (%)
Place of origin	
Rural	459 (58)
Urban (10 biggest cities)	329 (42)
Addis Ababa	218 (28)
Age, years	
<30	19 (3)
30–39	135 (17)
40–49	246 (31)
50–59	215 (27)
≥60	173 (22)
Menopausal status	
Premenopausal	178 (23)
Postmenopausal	610 (77)
Number of children, mean ±SD	6.09 ±3.1
Marriage	
At age ≤18 years	664 (84)
After age of 18 years	44 (6)
Unmarried	8 (1)
Unknown	72 (9)
Sexual partners (ever)	
None	1 (1)
One	407 (52)
Few (2–3)	120 (15)
Multiple (>3)	178 (22)
Unknown	82 (10)
Contraception	
Oral combined contraceptives	162 (21)
Depot-medroxyprogesterone-acetate injections	52 (7)
Other	13 (2)
None	522 (66)
Unknown	39 (5)
HIV status	
Known positive	86 (11)
Known negative	118 (15)
Not screened/negative	584 (74)
ECOG performance status at presentation	
ECOG 0	3 (1)
ECOG 1	440 (56)
ECOG 2	242 (31)
ECOG 3	95 (12)
ECOG 4	8 (1)
Stage of FIGO at start of RT	
Radical RT	
IIA	3 (1)
IIB	160 (20)
IIIA	17 (2)
IIIB	365 (46)
IVA	24 (3)
Nonradical RT	
IIIB	96 (12)
IVA	76 (10)
IVB	47 (6)
Single-fraction RT	
IIIB	96 (12)
IVA	76 (10)
IVB	47 (6)
Histology	
Squamous cell carcinoma	751 (95)
Adenocarcinoma	29 (4)
Other	8 (1)
Grading	
G1–G2	123 (16)
G3–G4	50 (6)
Not done	615 (78)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; RT, radiotherapy; SD, standard deviation.

were correctly assigned to RT according to local guidelines. Dose-specific survival analysis was performed based on the assigned RT schedule. One hundred eighty patients received radical RT, 389 patients were assigned to nonradical RT, and 219 patients received palliative single fractions.

Patient Characteristics

As shown in Table 1, most patients originated from rural Ethiopia (58%). The mean age was 49 years (22–91 years). Parity ranged from 0 to 17 children. One sexual partner in the patient's lifetime and early marriage at the age of 18 years or younger were reported in the majority of cases (52% and 84%, respectively). Contraception was used by 29% of patients. More than one tenth of the patients were known to be HIV positive. The high rate of 74% of patients with unknown HIV status is because within the first 3 years of data collection, screening was only done for patients with high risk history (e.g., HIV-positive family members or other HIV-defining diseases). Most patients presented with lightly restricted performance status (56%) and histologically confirmed squamous cell carcinoma (95%). FIGO stages IIIB–IVA at the time of RT were very common (71%).

Adherence and Supportive Treatment

Among patients assigned to radical RT, 49% received the recommended dose of 72 Gy or more. In case of nonradical RT, the rate of adherence was higher, and 83% received the recommended dose of 44 Gy. However, 10% received a higher dose of radiation than the recommended maximum of 50 Gy. Most palliative patients received two single fractions of 10 Gy each (53%).

For the whole cohort, reasons for discontinuation of an ongoing RT schedule were reported in 32 out of 159 cases of discontinuation. Half of these 32 patients discontinued because of radiation toxicities. Twenty-two percent did not return for RT for financial or logistical reasons. One patient with FIGO stage

IIB discontinued her second phase of radical RT because of breakdown of the Cobalt-60 unit.

Only 15% of all patients received at least one cycle of chemotherapy (50–60 mg/m^2 cisplatin and 500 mg/m^2 5-fluoruracil). Out of the 219 palliative patients, chemotherapy was administered in only 12 cases.

At the time of presentation, 90% of all patients suffered from abdominal pain, which was severe in 121 cases. However, morphine injections were given to only 14% of all patients, and tramadol was administered to 43% of all patients. Four percent of all patients received paracetamol only. Two hundred twenty-one patients with abdominal pain did not receive any analgesic.

Toxicities

As shown in Table 2, radiation dermatitis and diarrhea occurred in 9% and 12%, respectively, of the 610 patients who returned for a first follow-up within 3 months after RT ended. Half of the patients who suffered from vomiting previously received chemotherapy.

Late adverse effects were documented more often, partly because of additional information via phone calls. Among 440 patients with available follow-up data, 31% suffered from radiation proctitis. Subcutaneous fibrosis of the suprapubic tissue was very common (41%), and vaginal strictures occurred in 14% of the cases. Twenty-three percent of patients who returned for follow-up after 3 months after RT ended were incontinent, mostly because of vesicovaginal fistula (18%). Almost half of all patients with late follow-up information suffered from dysuria. Severe acute toxicities were observed in 5% of the 610 patients at the time of first follow-up, and severe late toxicities were seen in 10% of the 440 cases with late follow-up information. No life-threatening events because of radiation were reported.

Survival According to Adherence

A total of 154 deaths were registered within the cohort of 788 patients. For the worst-case scenario, the number increased to 448. As displayed in Table 3, the estimated overall survival after 1 and 2 years was 84% and 64%, respectively, and decreased to 54% and 35% in the assumption of worst-case scenario. The median survival time of 33 months in the main analysis declined to 14 months in the worst-case analysis.

Regarding adherence, patients had lower survival probabilities in the case of discontinuation (see Fig. 3). The most favorable 1-year overall survival was seen in patients who completed radical RT (96%). For those who discontinued, it decreased to 89% (HR, 1.3; 95% CI, 0.5–3.3, and HR, 1.5; 95% CI, 0.9–2.8) in the main and worst-case analyses, respectively). Patients who received the recommended dose of 44–50 Gy for nonradical RT had 1- and 2-year survival rates of 87% and 63%. In cases of discontinuation, survival dropped to 71% and 42%, respectively (HR, 3.1; 95%, CI 1.4–6.9; $p < .01$) However, for nonradical RT, survival did not differ significantly with a further increase of the total dose of radiation up to 76 Gy. For palliation, single fractions of 10 Gy each were administered. The estimated 1-year overall survival for patients with one single fraction was the least favorable within the whole cohort (14% in the main and 3% in the worst-case analysis). These patients were 7.3 times (95% CI, 3.3–16) more likely to die compared with patients with more single fractions.

Table 2. Incidence of early and late adverse effects graded according to Common Terminology Criteria for Adverse Events [15]

Adverse effects	Grade 1/2, *n* (%)	Grade 3/4, *n* (%)
Acute adverse effects ($n = 610$)		
Dermatitis	20/32 (8)	1/0 (1)
Diarrhea	7/55 (10)	10/0 (2)
Fatigue	0/27 (4)	18/0 (3)
Vomiting (grade not specified)	133 (22)	
Late adverse effects ($n = 440$)		
Proctitis	83/48 (30)	3/0 (1)
Suprapubic fibrosis	65/90 (36)	24/0 (5)
Urinary incontinence	46/50 (22)	4/0 (1)
Vesicovaginal fistula	22/50 (17)	5/0 (1)
Vaginal stricture	20/37 (13)	6/0 (1)
Noninfective cystitis	129/61 (43)	2/0 (1)

Early adverse effects were documented within 3 months after the end of radiotherapy ($n = 610$). The incidence of late adverse effects is based on the total of 440 patients who returned for follow-up afterwards.

Among the other variables included in the Cox model, only the comparison of no anemia and grade 1 anemia for radical (HR, 0.3; 95% CI, 0.1–0.9) and nonradical RT (HR, 0.4; 95% CI, 0.2–0.7) and the comparison of grade 1 and grade 2 anemia for nonradical RT (HR, 0.5; 95% CI, 0.3–0.9) were significantly relevant for prognosis in the worst-case analysis.

Discussion

This is the first study from sub-Saharan Africa to report on the discontinuation of RT affecting outcome in a large cohort of patients with CC in Ethiopia. In the case of adherence to guideline-conforming RT, patients at TAHRC had the best outcome.

Among patients assigned to radical and nonradical RT, 49% and 17%, respectively, discontinued their RT schedules and had lower chances of survival. Most known discontinuations were because of radiation toxicities. Hence, supportive therapies and brachytherapy are urgently needed. However, a larger number of patients discontinued for undocumented reasons, most likely financial and logistical obstacles [18, 19] or breakdown of the RT machine. Socioeconomic support for patients in need, reliable maintenance services with available spare parts, and more RT machines are necessary for better therapy adherence.

The advantage in survival of adherent patients might reflect a possible dose effect of RT. However, we assume that there was a certain selection bias toward the nonadherence group because of prognosis-relevant conditions that may have led to discontinuation of RT, which were not consistently reported (e.g., tumor progression, socioeconomic background of the patients). Unexpectedly, patients treated with nonradical RT seemingly did not benefit from a further dose increase above the recommended threshold. A possible explanation is that higher doses were administered in case of more aggressive and thus radiotherapy-resistant tumors.

Mostly because of methodological shortcomings, studies on a radiation dose-response relation for patients with CC have

Table 3. Overall survival of patients according to total doses of radiation received in main and worst-case Kaplan-Meier analyses

Radiation schedule: total dose of radiation received	Overall survival				Hazard ratios		
	Main % (95% CI)		Worst-case analysis, % (95% CI)				
	1-y OS	2-y OS	1-y OS	2-y OS	Total doses in comparison	Main analysis, HR (95% CI)	Worst-case analysis, HR (95% CI)
Total cohort ($n = 788$)	84 (80–87)	64 (58–69)	54 (50–57)	35 (31–39)			
Radical RT							
14–70 Gy ($n = 92$)	89 (81–96)	80 (68–92)	75 (66–85)	58 (44–71)	14–70 Gy vs. 72 or 76 Gy	1.3 (0.5–3.3)	1.5 (0.9–2.8)
72 or 76 Gy ($n = 88$)	96 (92–100)	83 (71–95)	91 (84–97)	69 (56–83)			
Nonradical RT							
4–42 Gy ($n = 67$)	71 (57–85)	42 (23–45)	34 (22–45)	19 (8–29)	4–42 Gy vs. 44–50 Gy	3.1[a] (1.4–6.9)	2.8[a] (1.7–4.6)
44–50 Gy ($n = 283$)	87 (82–92)	63 (54–73)	66 (60–72)	41 (33–48)	44–50 Gy vs. 53–76 Gy	1.2 (0.6–2.3)	1 (0.6–1.5)
53–76 Gy ($n = 39$)	89 (78–100)	69 (49–90)	61 (45–77)	40 (23–56)			
Single-fraction RT							
8–10 Gy ($n = 71$)	14 (0–33)	0	3 (0–8)	0	8–10 Gy vs. 20–42 Gy	7.3[a] (3.3–16)	2.5[a] (1.8–3.5)
20–42 Gy ($n = 148$)	73 (60–87)	44 (24–65)	24 (16–32)	13 (6–20)			

Hazard ratios according to total doses of radiation received, adjusted for grade of anemia, HIV status, estimated glomerular filtration rate, and performance status in Cox regression model.

[a]Statistically significant; $p < .05$.

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; RT, radiotherapy.

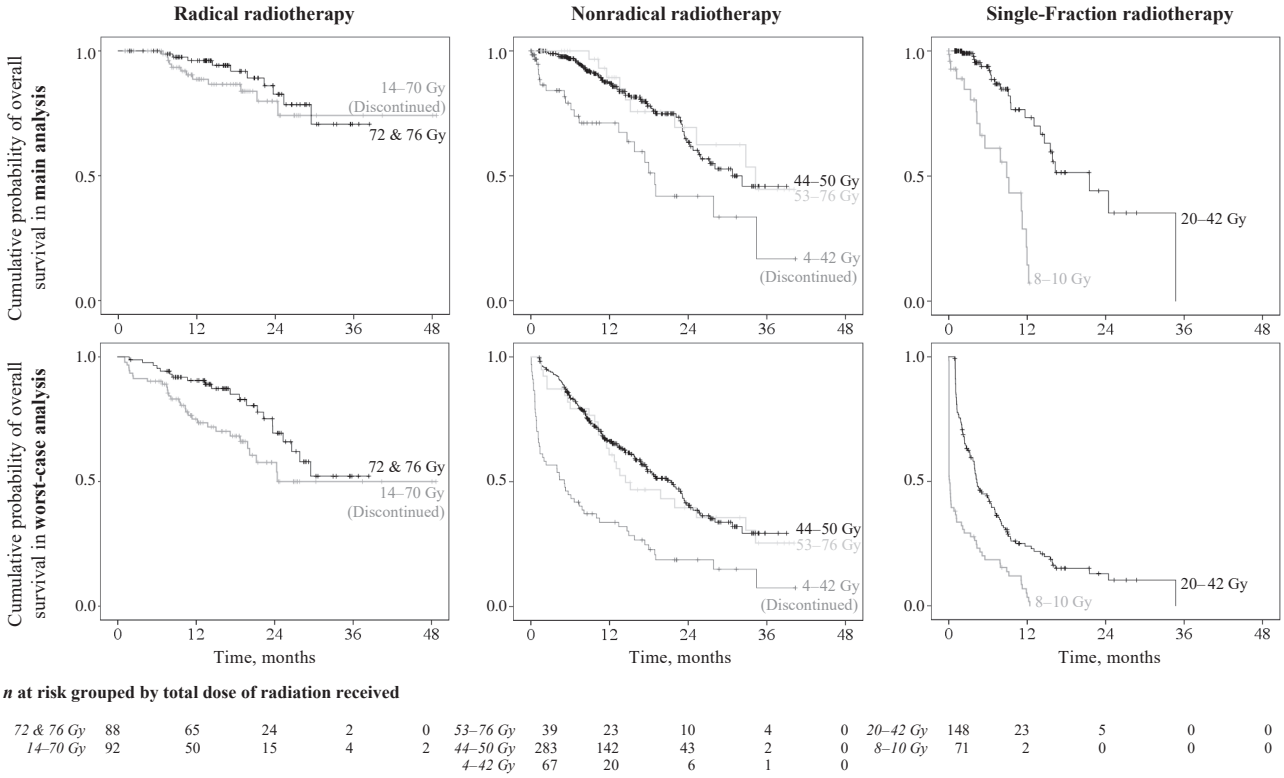


Figure 3. Overall survival of patients according to their radiotherapy schedules, grouped by total doses of radiation received, in the main and worst-case Kaplan-Meier analyses.

had controversial outcomes [20]. However, in the case of RT for prostate cancer, there is clear proof for better survival when a certain dose threshold (78–80 Gy) is reached [21]. Correspondingly, Beskow et al. demonstrated better survival along with dose increase for patients with CC [22].

We found very few studies reporting on the survival of patients with CC after sole EBRT because the standard of care is a combination of EBRT and ICBT for FIGO stages IB2 or IIB–IVA [23]. Several authors describe a RT pattern with Cobalt-60 similar to the radical RT schedule at TAHRC; however, this was not

restricted to FIGO stages IIA–IIIA [24–27]. A prognostic benefit for patients with FIGO stage IIIB by increasing the total dose up to 85 Gy has been demonstrated [20, 28]. A large Brazilian study on RT for patients with CC at FIGO stage IIIB ($n = 202$) compared different doses of radiation delivered by a LINAC without IBRT. The authors reported a 5-year survival of almost 30% after RT with a total dose of 60 or 70 Gy, compared with significantly lower survival rates for patients who received EBRT with lower doses [29]. However, access to RT at TAHRC is limited. Hypofractionation, as in the nonradical schedule for patients with FIGO stages IIIB and IVA, comes with the advantage of a lower number of treatment days (a maximum of 14 fractions compared with 36 fractions for radical RT) and allows a larger number of patients to be treated.

Regarding the adverse effects that occurred, no grade 4 toxicity was seen, and grade 3 toxicities occurred in 5% of patients within 3 months after RT and in 10% afterward. Compared with the respective highest rates reported by other studies, late adverse effects at TAHRC were seen more frequently and acute adverse effects less frequently.

Other studies have reported lower rates for any-grade radiation proctitis (17% [26]), urinary incontinence (20% [30]), vesicovaginal fistulae (13% [30]), noninfective cystitis (20% [26]), and suprapubic fibrosis (24% [31]) than the respective 31%, 23%, 18%, 44%, and 41% from our study sample. Vaginal strictures appear to be associated with higher age and treatment with ICBT [31, 32]. As ICBT was not available at TAHRC, a lower rate of 14% was found, compared with the 34% reported by Saibishkumar et al. [31].

Regarding acute adverse effects, the highest rate for radiation dermatitis found in literature was 17% [32], which is twofold the rate of dermatitis occurring at TAHRC. For radiation diarrhea, rates up to 65% have been reported [27], whereas we found a low rate of 12%, most probably because of underdiagnosing at TAHRC and the less frequent administration of chemotherapy.

Measured by international guidelines [4, 23], RT for CC at TAHRC was suboptimal in four respects in addition to the described negative effect of nonadherence on outcome: (a) no ICBT was used, (b) no LINAC was available for EBRT, (c) advanced stages of CC received lower doses than internationally recommended because of the lack of capacities, and (d) the generally recommended addition of chemotherapy to radiation was only realized in 15% of all patients.

The relevance of ICBT for primary endpoints such as survival and toxicity has been well established by numerous studies. A large cohort study by Han et al. included 7,359 patients with CC and reported significantly higher survival rates for patients who received ICBT compared with those who did not (58% vs. 46%, respectively) [33]. Similarly, ICBT has been applied successfully in low-resource settings [32, 34–36]. At the time of publishing, brachytherapy services have finally been installed and used daily at TAHRC.

Concerning the lack of LINACs at TAHRC, their role as the optimal and most targeted RT modality for deep-seated tumors such as CC is generally accepted. The advantageous role of LINACs is marked by higher percent depth dose and dose rate, lower skin dose, sharper beam, and therefore fewer radiation-associated adverse effects. However, we should question the feasibility of LINACs in a setting without reliable electricity and with a small number of well-trained staff members.

At TAHRC, most patients included in the present study were FIGO stage IIIB, which has been shown to respond well to high-dosage EBRT [20, 28]. However, these patients received a low-dose nonradical RT, which allowed more patients to be treated by saving radiation capacities. To that end, the limited availability of RT, regardless of its modality, is the main obstacle for adequate RT in Ethiopia and needs to be addressed. In Africa, Ethiopia has the second largest gap, after Nigeria, between the availability of and demand for RT machines. Judging from the WHO recommendations, there are 73 RT units missing in Ethiopia [10]. This serious quantitative deficit should be addressed first, before insularly enhancing RT quality with complex techniques.

Regarding chemoradiation, most patients at TAHRC did not receive the recommended concurrent or palliative chemotherapy along with RT. The facts that a larger proportion of patients with cancer in sub-Saharan Africa might not be fit for platin-based chemotherapy [37] and that adverse effects can be difficult to control do not sufficiently explain the lack of chemotherapy in 85% of all patients observed. Our findings point toward mainly financial obstacles that interfere with clinical indications. Hence, we emphasize the importance of available and affordable chemotherapy for all patients with CC. For palliation, chemotherapy including cisplatin, paclitaxel and/or bevacizumab is the standard of care according to international guidelines [4, 23]. At TAHRC, in a setting of limited availability and finances, only 6% of palliative patients received additional chemotherapy. The more affordable monthly palliative single-fraction RT has proved effective since the late 1970s in cessation of bleeding and pain, although serious complications have occurred [38].

Our results are limited by the retrospective nature of the study. First, we were unable to ascertain whether patients discontinued RT because of substandard care, and correspondingly survival tragically decreased, or whether patients discontinued RT because of fatal progression of the disease, and survival inevitably decreased. A prospective interventional study to compare adherence with discontinuation (substandard care) is ethically not feasible. Hence, this kind of retrospective data will be the only source of information for observing the effects of substandard care. Second, AIDS not only leads to significantly lower survival rates in patients with CC [39] but also has negative effects on therapy adherence [40]. As only 26% of patients included were screened for HIV, we were not able to fully control for HIV status in the multivariate analysis. Third, adverse effects, as a possible reason for discontinuation, were not documented in a prospective, standardized way. We expect that the actual number of adverse effects was higher than documented. Physicians did not precisely inquire about and document side effects because therapeutic measures were unavailable. Fourth, the low median follow-up time of 9.6 months, because of the 81% of patients who were lost to follow-up, limited our results. Most patients came from rural areas, where only 12% have access to electricity [41]. Hence, even if patients were alive, contact via telephone was rarely possible. The time and financial resources of this study did not allow us to contact each patient personally.

However, this study is the first large cohort study in the African continent to report in detail on RT schedules, adherence, survival, and adverse effects. Findings on the outcome of EBRT alone for CC without ICBT are of high interest for the still-numerous countries lacking ICBT.

Conclusion

In this study, data from 788 patients with cervical cancer treated according to the Ethiopian RT guidelines of 2008–2012 were retrospectively analyzed. Nonradical RT for late stages with total doses of 44–50 Gy was administered in most cases. We noted higher rates of late toxicities than comparable studies reported. Chemotherapy was administered to only 15% of all patients. Discontinuation of RT was associated with lower chances of survival. To enhance therapy adherence, socioeconomic support for patients in need, reliable maintenance services, and supportive therapies are necessary. Chemotherapy and analgesics need to be available and affordable. Besides guideline-conforming treatment, mere access to RT is extremely limited. To assure standard radical RT for all FIGO stages up to IVA, more RT facilities are needed to provide more radiation time. Additionally, ICBT must be implemented to reduce the adverse effects associated with Cobalt-60 alone.

Acknowledgments

The authors are grateful for the dedicated work of the entire staff at the oncology ward at Tikur Anbessa Hospital. The authors would especially like to thank their study nurse, Tinsae Gelatae, for conducting follow-up phone calls in Amharic and Oromo; their colleague Timotewos Genebo for logistical support far beyond his responsibilities, and Mrs. Mulu and Mr. Neme for searching and retrieving the archived patient files. This study was supported by the Federal Ministry of Research and Education of Germany, grant 01DG12006.

Author Contributions

Conception/design: Ulrike Moelle, Adamu Addissie, Christoph Thomssen, Dirk Vordermark; Eva J. Kantelhardt
Provision of study material or patients: Assefa Mathewos, Abreha Aynalem, Tigeneh Wondemagegnehu, Bekuretsion Yonas
Collection and/or assembly of data: Ulrike Moelle, Mathias Begoihn
Data analysis and interpretation: Ulrike Moelle, Assefa Mathewos, Susanne Unverzagt, Ahmedin Jemal, Eva J. Kantelhardt
Manuscript writing: Ulrike Moelle, Ahmedin Jemal, Eva J. Kantelhardt
Final approval of manuscript: Ulrike Moelle, Assefa Mathewos, Abreha Aynalem, Tigeneh Wondemagegnehu, Bekuretsion Yonas, Adamu Addissie, Susanne Unverzagt, Ahmedin Jemal, Christoph Thomssen, Dirk Vordermark; Eva J. Kantelhardt

Disclosures

The authors indicated no financial relationships.

References

1. Jemal A, Bray F, Forman D et al. Cancer burden in Africa and opportunities for prevention. Cancer 2012;118:4372–4384.

2. Torre LA, Siegel RL, Ward EM et al. Global cancer incidence and mortality rates and trends–An update. Cancer Epidemiol Biomarkers Prev 2016; 25;16–27.

3. Arbyn M, Castellsagué X, de Sanjosé S et al. Worldwide burden of cervical cancer in 2008. Ann Oncol 2011;22:2675–2686.

4. Oaknin A, Rubio MJ, Redondo A et al. SEOM guidelines for cervical cancer. Clin Transl Oncol 2015; 17:1036–1042.

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

6. Sankaranarayanan R, Ferlay J. Worldwide burden of gynaecological cancer: The size of the problem. Best Pract Res Clin Obstet Gynaecol 2006;20: 207–225.

7. Zubizarreta EH, Fidarova E, Healy B et al. Need for radiotherapy in low and middle income countries – The silent crisis continues. Clin Oncol (R Coll Radiol) 2015;27:107–114.

8. Portelance L, Chao KC, Grigsby PW et al. Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. Int J Radiat Oncol Biol Phys 2001;51: 261–266.

9. van Dyk J, Battista JJ. Cobalt-60: An old modality, a renewed challenge. Curr Oncol 1996;3:8–17.

10. Abdel-Wahab M, Bourque JM, Pynda Y et al. Status of radiotherapy resources in Africa: An International Atomic Energy Agency analysis. Lancet Oncol 2013;14:e168–e175.

11. Population projection values of 2015 at zonal and wereda levels by urban and rural residence and by sex. In: Population Projection of Ethiopia for All Regions at Wereda Level from 2014–2017. Addis Ababa, Ethiopia: Central Statistical Agency, Federal Democratic Republic of Ethiopia; August 2013:60.

12. Ethiopia (2012): Estimated incidence and prevalence, adult population: Female. In: Ferlay J, Soerjomataram I, Ervik M et al. GLOBOCAN 2012 version 1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013. Available at http://globocan.iarc.fr. Accessed on March 2, 2016.

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

14. Sharma V, Gaye PM, Wahab SA et al. Patterns of practice of palliative radiotherapy in Africa, Part 1: Bone and brain metastases. Int J Radiat Oncol Biol Phys 2008;70:1195–1201.

15. National Cancer Institute. Common Terminology Criteria for Adverse Events. Version 4.0. Rockville, MD: National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services; May 29, 2009:3–194.

16. Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. Int J Gynecol Obstet 2009;105:107–108.

17. Cox DR, Oakes D. *Analysis of Survival Data*. Boca Raton, LA: Chapman & Hall/CRC Press; 1984.

18. Hailu A, Mariam DH. Patient side cost and its predictors for cervical cancer in Ethiopia: A cross sectional hospital based study. BMC Cancer 2013;13:69.

19. Akinlade BI, Folasire AM, Elumelu-Kupoluyi TN et al. Radiation therapy interruption in a poor resource setting: Causes and management. Afr J Med Med Sci 2014;43:333–337.

20. Petereit DG, Pearcey R. Literature analysis of high dose rate brachytherapy fractionation schedules in the treatment of cervical cancer: Is there an optimal fractionation schedule? Int J Radiat Oncol Biol Phys 1999;43:359–366.

21. Eade TN, Hanlon AL, Horwitz EM et al. What dose of external-beam radiation is high enough for prostate cancer? Int J Radiat Oncol Biol Phys 2007; 68:682–689.

22. Beskow C, Agren-Cronqvist AK, Lewensohn R et al. Biological effective dose evaluation and assessment of rectal and bladder complications for cervical cancer treated with radiotherapy and surgery. J Contemp Brachytherapy 2012;4:205–212.

23. Colombo N, Carinelli S, Colombo A et al. Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23(suppl 7):vii27–vii32.

24. Logsdon MD, Eifel PJ. FIGO IIIB squamous cell carcinoma of the cervix: An analysis of prognostic factors emphasizing the balance between external beam and intracavitary radiation therapy. Int J Radiat Oncol Biol Phys 1999;43:763–775.

25. Akine Y, Hashida I, Kajiura Y et al. Carcinoma of the uterine cervix treated with external irradiation alone. Int J Radiat Oncol Biol Phys 1986;12: 1611–1616.

26. Lei ZZ, He FZ. External cobalt 60 irradiation alone for stage IIB carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 1989;16:339–341.

27. Koeck GP, Jacobson LE, Hillsinger WR. Results of cobalt 60 rotation therapy in carcinoma of the cervix. Am J Roentgenol Radium Ther Nucl Med 1966; 96:81–91.

28. Lanciano RM, Won M, Coia LR et al. Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: A final report of the 1973 and 1978 Patterns of Care Studies. Int J Radiat Oncol Biol Phys 1991;20:667–676.

29. Ferreira PR, Braga-Filho A, Barletta A et al. Radiation therapy alone in stage III-B cancer of the uterine cervix–A 17-year experience in southern Brazil. Int J Radiat Oncol Biol Phys 1999;45: 441–446.

30. Elghamrawi KA, Haggag MH, Habib EE. Treatment complications among long-term survivors of cervical cancer: Treated by surgery or radiotherapy. Oncol Rev 2011;5:261–266.

31. Saibishkumar EP, Patel FD, Sharma SC. Evaluation of late toxicities of patients with carcinoma of the cervix treated with radical radiotherapy: An audit from India. Clin Oncol (R Coll Radiol) 2006;18: 30–37.

32. Arulponni TR, Janaki MG, Nirmala S et al. Carcinoma cervix treated with radiotherapy - Our experience with emphasis on our concerns. J Obstet Gynaecol India 2010;60:61–65.

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

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

35. Ferrigno R, Campos de Oliveira Faria SL, Weltman E et al. Radiotherapy alone in the treatment of uterine cervix cancer with telecobalt and low-dose-rate brachytherapy: Retrospective analysis of results and variables. Int J Radiat Oncol Biol Phys 2003;55:695–706.

36. Levin CV, El Gueddari B, Meghzifene A. Radiation therapy in Africa: Distribution and equipment. Radiother Oncol 1999;52:79–83.

37. McArdle O, Kigula-Mugambe JB. Contraindications to cisplatin based chemotherapy in the treatment of cervical cancer in sub-Saharan Africa. Radiother Oncol 2007;83:94–96.

38. Smith SC, Koh WJ. Palliative radiation therapy for gynaecological malignancies. Best Pract Res Clin Obstet Gynaecol 2001;15:265–278.

39. Maiman M, Fruchter RG, Guy L et al. Human immunodeficiency virus infection and invasive cervical carcinoma. Cancer 1993;71:402–406.

40. Ngugi P. *Response and Adherence of HIV Positive Women to Cervical Cancer Treatment* [master's thesis]. Port Elizabeth, South Africa: Nelson Mandela Metropolitan University; 2011.

41. Access to electricity (% of population): Ethiopia, 1991–2014. Sustainable Energy for All (SE4ALL) database from the SE4ALL Global Tracking Framework led jointly by the World Bank, International Energy Agency, and the Energy Sector Management Assistance Program. In: World Bank Open Data. Washington, D.C.: World Bank. Available at https://data.worldbank.org/indicator/EG.ELC.ACCS.ZS?locations=ET. Accessed November 19, 2017.

For Further Reading:
Kathleen R. Ragan, Natasha Buchanan Lunsford, Judith Lee Smith et al. Perspectives of Screening-Eligible Women and Male Partners on Benefits of and Barriers to Treatment for Precancerous Lesions and Cervical Cancer in Kenya. ***The Oncologist*** 2018;23:35-43.

Implications for Practice:
This article provides important insight into female and male partner perspectives regarding benefits, facilitators, and barriers to treatment for precancerous lesions and cervical cancer. These novel research findings can inform the development of targeted community health interventions, educational messages, and resources and aid stakeholders in strengthening strategic plans regarding treatment coverage and cervical cancer prevention. Because several treatment barriers identified in this study are similar to barriers associated with cervical cancer screening in low- and middle-resourced countries, effective messaging interventions could address barriers to receipt of both screening and treatment.

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.

Berlin, 28.02.2024 Matthias Begoihn

Danksagungen

Mein Dank gilt an erster Stelle meiner Betreuerin Prof. Dr. Eva Kantelhardt. Ohne ihre langjährige Unterstützung beim Verfassen der Publikationen und dieser Dissertation sowie der logistischen und organisatorischen Hilfestellung in Äthiopien wäre diese Arbeit nicht möglich gewesen.

Ich bedanke mich bei Ulrike Moelle, mit der ich die Daten in Äthiopien gesammelt habe, für die intensive und arbeitsreiche Zeit in Addis. Mein Dank gilt den Kolleg*innen des Tikkur Anbessa Specialized Hospital in Addis Abeba: Dr. Mathewoes und Dr. Wondemagegnehu aus der Abteilung für Strahlentherapie sowie Dr. Hezkiel Petros aus der Abteilung für Gynäkologie für die professionelle und gute Zusammenarbeit sowie Mulu und Neme für das Sammeln und Bereitstellen der Akten. Bei Etagegne bedanke ich mich herzlich für ihre Gastfreundschaft, die inspirierenden Gespräche und die Einführung in die grandiose äthiopische Küche.

Apl. Prof. Dr. Andreas Wienke danke ich für seine Expertise bei methodischen und statistischen Fragestellungen.

Nicht zuletzt danke ich den wichtigsten Personen, die mein Leben bereichern: meiner Familie, meiner Partnerin und meinen Freunden.

In Erinnerung an die zu früh verstorbenen Dr. Aynalem und Herrn Timotewos.