Medizinische Fakultät der Martin-Luther-Universität Halle-Wittenberg

Charakteristika und Verlauf von Frauen mit gynäkologischen Malignomen in Addis Abeba, Äthiopien, am Beispiel Ovarialkarzinom und Vulvakarzinom

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

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

von Swantje Piszczan
geboren am 18.06.1991 in Westerstede

Betreuerin: PD Dr. med. Eva Johanna Kantelhardt

Gutachterin/ Gutachter:
Frau Prof. P. Wimberger, Dresden
PD F. Bartel

21.01.2021
30.06.2021

Referat

In dieser Arbeit werden zusammenfassend die Ergebnisse von zwei Studien dargestellt. In der ersten Studie wurden die klinischen Charakteristika und das Überleben von Patientinnen mit malignen Ovarialtumoren in Addis Abeba, Äthiopien, im Rahmen einer retrospektiven Kohortenstudie untersucht. In der zweiten Studie wurden die Ergebnisse einer retrospektiven Kohortenstudie zu Charakteristika und Überleben von Patientinnen mit Vulvakarzinom (Promotion Herr Kröber) in Addis Abeba dargestellt. Ziel der Arbeit war die epidemiologische Beschreibung der Krankheitslast und der klinischen Versorgung bisher wenig beschriebener gynäkologischer Krebserkrankungen in Addis Abeba durch eine häufige Krebsentität (maligne Ovarialtumoren) in Zusammenschau mit einer eher seltenen Krebsentität (Vulvakarzinom).

Das Ovarialkarzinom war im Jahr 2012 die dritthäufigste Krebsentität bei Frauen in Äthiopien mit geschätzten 2550 Neudiagnosen und 2000 Todesfällen. Das mediane Erkrankungsalter bei Erstdiagnose in der untersuchten Kohorte betrug 47 Jahre. Die geschätzten 1- und 2-Jahres-Überlebensraten betrugen 78 % bzw. 59 %. Von den Patientinnen mit verfügbarem Histologie-Befund zeigten 73 % ein epitheliales Karzinom. Knapp die Hälfte der Patientinnen befanden sich bei Diagnosestellung in FIGO Stadium III oder IV (limitierte Bewertung durch eingeschränkte Diagnostik). Eine operative Therapie erhielten ca. 80 % der Patientinnen; platinhaltige Chemotherapie erhielten 59 % bei zum Teil eingeschränkter Verfügbarkeit. Patientinnen mit postoperativen Residualtumoren hatten ein höheres Risiko zu versterben (HR= 2.23; 95 % CI= 1.08–4.49). Trotz fortgeschrittenen Stadiums erhielten nur 29 % der Patientinnen eine supportive Therapie.

Die altersstandardisierte Inzidenz des Vulvakarzinoms in Äthiopien lag bei 1,5/100.000. Das mediane Alter der Kohorte zum Zeitpunkt der Erstdiagnose lag bei 39 Jahren. Die 1- bzw. 2-Jahres-Überlebensraten betrugen 80 % bzw. 51 %. Patientinnen, die eine der drei verfügbaren Therapieoptionen Strahlentherapie (HR= 0,36; 95 % KI= (0,14–0,90)), operative Therapie (HR= 0,44; 95 % KI= (0,19–1,03)) oder Chemotherapie (HR= 0,42; 95 % KI= (0,15–1,12)) erhielten, hatten tendenziell eine verlängerte Überlebenszeit. Etwa 57 % der Patientinnen waren HIV-positiv.

Die Ergebnisse wurden mit Daten aus anderen Ländern Afrikas sowie aus Westeuropa und den USA verglichen. Trotz einer relativ hohen Anzahl von Tumoren mit guter Prognose war das Überleben vergleichsweise niedrig. Dies zeigt die deutliche Notwendigkeit, die Verfügbarkeit und Qualität von Diagnostik und Therapie zu verbessern. Diese Arbeit stellt Evidenz für Handlungsempfehlungen zur besseren Gesundheitsversorgung in der Region zur Verfügung.

Piszczan, Swantje: Charakteristika und Verlauf von Frauen mit gynäkologischen Malignomen in Addis Abeba, Äthiopien, am Beispiel Ovarialkarzinom und Vulvakarzinom. Halle (Saale), Univ., Med. Fak., Diss., 15 Seiten, 2020

Report

This dissertation summarizes the results of two explorative studies. The first retrospective cohort study summarized clinical characteristics and survival of patients with malignant ovarian tumors in Addis Ababa, Ethiopia, based on clinical and population-based data. The second study analyzed characteristics and survival of patients with vulvar cancer in Addis Ababa. The objective of this study is to describe the disease burden and clinical treatment of gynecological cancers in Ethiopia by looking at a common cancer entity (malignant ovarian tumors) and a rather rare cancer entity (vulvar cancer).

In 2012, ovarian cancer was the third most common cancer entity among women in Ethiopia, with about 2,550 diagnosed cases and 2,000 deaths. The median age at the point of diagnosis in this cohort was 47 years. The estimated 1- and 2-year overall survival rates were 78 % and 59 %, respectively. Of patients with histologic result available, 73 % had epithelial cancers. Almost half were classified as FIGO stage III or IV (assessment limited due to few diagnostic options). Four out of five patients received surgery, 59 % of all patients received a platin-based chemotherapy due to limited availability. Patients with residual tumor after surgery showed worse survival outcome (HR, 2.23; 95 % CI 1.08–4.49). Despite a high number of advanced stage diseases, supportive therapy was given to 29 % only.

The age-standardized incidence rate of vulvar cancer in Ethiopia was 1.5/100,000. The median age at the point of diagnosis was 39 years. The estimated 1- and 2-year overall survival rates were 81 % and 51 %, respectively. Patients who received therapy options radiotherapy (HR= 0.36; 95 % CI=(0.14–0.90), surgery (HR= 0.44; 95 % CI=(0.19–1.03)) or chemotherapy (HR= 0.42; 95 % CI=(0.15–1.12)) tended to have prolonged survival time. About 57 % of patients were HIV-positive.

The results were compared to data from other African countries as well as Western Europe and the U.S.. Despite a high number of tumors with expected good prognosis, the survival rates were comparatively low. This clearly indicates the need of increasing the availability and quality of diagnostic and therapeutic standards. The findings are discussed and translated into practical advice to improve the quality of health care in the region.

Piszczan, Swantje: Charakteristika und Verlauf von Frauen mit gynäkologischen Malignomen in Addis Abeba, Äthiopien, am Beispiel Ovarialkarzinom und Vulvakarzinom. Halle (Saale), Univ., Med. Fak., Diss., 15 Seiten, 2020

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Verzeichnis der Abkürzungen und Symbole

FIGO – International Federation of Gynecology and Obstetrics

HIV – Humanes Immundefizienz-Virus

HPV – Humanes Papillomavirus

HR – Hazard Ratio

KI – Konfidenzintervall

OP – Operation

WHO – World Health Organization

1. Einleitung und Zielstellung

Chronische Erkrankungen machen heute weltweit den Großteil der Gesundheitsprobleme aus und nehmen im globalen Fokus einen zunehmend größeren Stellenwert ein. In den letzten Jahrzehnten stieg die Krankheitslast durch chronische Erkrankungen sowohl in Ländern mit hohem Einkommen als auch in Ländern mit niedrigem und mittlerem Einkommen deutlich an [1]. Die Reduktion der Mortalität durch diese Erkrankungen um ein Drittel bis 2030 ist eines der nachhaltigen Entwicklungsziele der WHO [2].

Mit weltweit über 18 Millionen Neuerkrankungen pro Jahr (2018) und mehr als 9 Millionen Todesfällen (2016) sind Krebserkrankungen nach den Herz-Kreislauf-Erkrankungen die zweithäufigste Ursache für Morbidität und Mortalität [1]. Durch Verbesserung der Lebensbedingungen und steigendes Alter der Bevölkerung nimmt die Anzahl der Krebserkrankungen auch in Ländern mit niedrigem und mittlerem Einkommen stetig zu [3]. In Afrika erkrankten 2018 mehr als eine Millionen Menschen an Krebs [4].

Gynäkologische Karzinome gehören in Afrika zu den häufigsten Tumorentitäten. Das Mammakarzinom und das Zervixkarzinom sind die häufigsten Karzinome und bereits Gegenstand vieler Forschungsarbeiten. Bei Frauen war das Ovarialkarzinom in Afrika in 2020 die fünfhäufigste Entität mit mehr als 24.000 Neudiagnosen [5]. Die Datenlage zum Ovarialkarzinom in Afrika ist bisher gering. Das Vulvakarzinom tritt im Vergleich zu den anderen gynäkologischen Tumoren eher selten auf und ist daher im afrikanischen Raum bisher kaum erforscht.

In dieser Dissertation wurden Frauen mit Ovarialkarzinom und Vulvakarzinom beispielhaft in Äthiopien untersucht. Äthiopien ist das zweitbevölkerungsreichste Land Afrikas mit einer Bevölkerungszahl von 112 Millionen (2019), davon sind 56 Millionen Frauen [6]. In Äthiopien leben 80% der Bevölkerung in ländlichen Gebieten [6]. Wie in vielen Ländern mit geringem Einkommen, sind die Diagnostik- und Therapiemöglichkeiten in Äthiopien limitiert und das Bewusstsein für Tumorerkrankungen als steigende Krankheitslast gering [7].

Die Belastung durch Krebserkrankungen lag 2018 bei mehr als 46.000 Neudiagnosen bei Frauen. Gynäkologische Tumore und das Mammakarzinom hatten einen Anteil von mehr als 50 % [4].

Das Ovarialkarzinom war zum Untersuchungszeitpunkt in Äthiopien die dritthäufigste Krebsentität bei Frauen mit geschätzten 2550 Neudiagnosen in 2012 [4]. In 2020 war das Ovarialkarzinom nach dem Mammakarzinom, dem Zervixkarzinom und dem Kolonkarzinom die vierthäufigste Tumorentität mit 2655 geschätzten Neudiagnosen [5]. Während in Ländern

mit hohem Einkommen die Inzidenzraten in den letzten Jahren sanken, kam es in Ländern mit mittlerem und niedrigem Einkommen, u.a. in Äthiopien, zu einer Zunahme. Das epitheliale Ovarialkarzinom ist mit Risikofaktoren wie einer geringen Anzahl von Geburten, höherem Lebensalter, Einnahme von Hormonersatztherapie und familiärer Prädisposition assoziiert [8]. Trotz der in Äthiopien hauptsächlich ländlichen Bevölkerungsstruktur sind diese Risikofaktoren in der urbanen Region Addis Abeba zunehmend.

Während das Mamma- und das Zervix-Karzinom durch Etablierung von Früherkennung und Screenings früher erkannt und behandelt werden können, wird das Ovarialkarzinom häufig erst in fortgeschrittenen Stadien diagnostiziert. Insbesondere in Ländern mit knappen Ressourcen wie Äthiopien stellen diese spät diagnostizierten Patientinnen eine Herausforderung für ein adäquates Staging sowie für Therapieplanung und -durchführung dar. Patientinnen in fortgeschrittenen Stadien benötigen gegebenenfalls eine palliative Versorgung und eine entsprechende Schmerztherapie.

Das Vulvakarzinom ist eine eher seltene Krebsentität, doch die Inzidenzraten stiegen weltweit in den letzten Jahren [9,10]. Mit einem Anteil von 90% ist das Plattenepithelkarzinom der häufigste histologische Typ [11]. Der Subtyp des keratinisierenden Plattenepithelkarzinoms tritt häufig bei älteren Frauen auf und ist assoziiert mit chronischen Erkrankungen wie Lichen sklerosus [12]. Das nicht-keratinisierende Plattenepithelkarzinom kommt vor allem im jüngeren Alter vor und weist eine Assoziation zu HPV- und HIV-Infektionen auf [13]. Diese Infektionserkrankungen sind insbesondere in Ländern mit mittlerem und niedrigem Einkommen verbreitet [14].

Im Rahmen dieser Arbeit haben wir Daten sowohl von Patientinnen mit malignen Ovarialtumoren als auch von Patientinnen mit Vulvakarzinom in Addis Abeba, Äthiopien, erhoben.

Die Kohorte der Patientinnen mit malignen Ovarialtumoren setzt sich zusammen aus Daten aus einem Universitätskrankenhaus und einem weiteren Krankenhaus in Addis Abeba und Daten aus dem Addis Ababa City Cancer Registry. In Zusammenarbeit mit den Ärzten des Tikur Anbessa Hospitals und des Zewditu Memorial Hospitals haben wir Patientenakten aus der Gynäkologie und Onkologie gesichtet und ausgewertet. Aus diesen klinischen Akten haben wir Daten zu Patientencharakteristika und klinischen Charakteristika erhoben. Zusätzlich haben wir Informationen zu Therapie und Überleben der Patientinnen gesammelt. Von 125 Patientinnen, die eine operative Therapie für ein histologisch gesichertes Ovarialkarzinom erhalten haben, wurden die Operationsberichte ausgewertet.

Aus den Krebsregisterdaten konnten wir Informationen zu Tumorhistologie, erhaltener Therapie und Überlebensstatus generieren. Das follow-up der Patientinnen aus beiden Gruppen wurde per Telefon durchgeführt und dabei Daten zum Überlebensstatus, evtl. weiterer erhaltener Therapie und ggf. zum Todeszeitpunkt erhoben.

Im Artikel „Clinical Characteristics and Survival of Patients with Malignant Ovarian Tumors in Addis Ababa, Ethiopia" in der Anlage A dieser Dissertation [15] wurden die Ergebnisse zu klinischen Charakteristika, Diagnostik, Therapie und Überleben von Patientinnen mit malignen Ovarialtumoren, die zwischen 2009 und 2015 in Addis Abeba diagnostiziert wurden, publiziert. Nach aktueller Recherche ist dies die bisher größte beschriebene klinische Kohorte von Frauen mit Ovarialkarzinom in Subsahara-Afrika.

Die Daten der Patientinnen mit Vulvakarzinom haben wir aus der onkologischen Abteilung des Black Lion Hospitals generiert. Dazu haben wir die klinischen Akten der dort behandelten Patientinnen gesichtet und Informationen zu klinischen Charakteristika, Therapie und Überleben erhoben. Das follow-up der Patientinnen wurde per Telefon durchgeführt.

In der Studie „Vulvar cancer in Ethiopia – A cohort study on the characteristics and survival of 86 patients" in der Anlage B dieser Dissertation [16] wurden die Ergebnisse der erhobenen Daten von Patientinnen mit Vulvakarzinom veröffentlicht. Dies war zum Veröffentlichungszeitpunkt die erste Studie zu Patientinnen mit Vulvakarzinom in Subsahara-Afrika.

Das internationale Bewusstsein für die Notwendigkeit der Verbesserung der onkologischen Versorgung in Afrika ist zunehmend. Dies zeigt sich auch durch die Veröffentlichung angepasster Leitlinien zu spezifischen Krebserkrankungen durch das National Comprehensive Cancer Network, deren Ziel es ist, die weltweite Versorgung von Krebspatientinnen zu verbessern [17].

Das Ziel dieser Arbeit ist die Beschreibung der Krankheitslast durch maligne Tumore des Ovars und der Vulva sowie deren klinischer Versorgung in Addis Abeba, Äthiopien. Dies soll dazu beitragen, die bisher spärliche Datenlage zu diesen Tumorerkrankungen in Afrika zu verbessern. Dazu wurden die Charakteristika und das Überleben von Patientinnen mit einer häufigen Krebsentität, den malignen Ovarialtumoren, und einer relativ seltenen, dem Vulvakarzinom, untersucht. Im Rahmen dieser Arbeit wurden folgende Fragestellungen bearbeitet:

1. Welche demographischen und klinischen Charakteristika zeigen Patientinnen mit malignen Ovarialtumoren in dieser klinischen Kohorte in Addis Abeba?

2. Wie ist der Zugang der Patientinnen mit malignen Ovarialtumoren zu Diagnostik und kurativen Therapieoptionen (Operation, Chemotherapie), sowie zu palliativer Versorgung und Schmerztherapie und welchen Einfluss haben erstgenannte auf das Überleben?

3. Wie hoch ist die 1- und 2-Jahres-Überlebenswahrscheinlichkeit von Patientinnen mit malignen Ovarialtumoren und wie verhalten sich diese Ergebnisse im regionalen Vergleich sowie zu Ergebnissen aus den USA und Westeuropa?

4. Welche demographischen und klinischen Charakteristika zeigen Patientinnen mit Vulvakarzinom in Addis Abeba und wie stellt sich das Überleben dar?

5. Wie viele Vulvakarzinompatientinnen erhalten die zur Verfügung stehenden Therapieoptionen (Operation, Chemotherapie, Strahlentherapie) und welchen Einfluss haben diese auf das Überleben?

Die Ergebnisse wurden mit Daten aus den USA und Westeuropa sowie aus anderen Ländern Subsahara-Afrikas verglichen. Mithilfe der gewonnenen Erkenntnisse soll die Evidenz für Handlungsempfehlungen zur Verbesserung der Gesundheitsversorgung in der Region Sub-Sahara-Afrika zur Verfügung gestellt werden.

Diese Dissertation basiert auf den im Anhang eingefügten Publikationen sowie auf der Zusammenarbeit zwischen der Martin-Luther-Universität Halle-Wittenberg und der Universität Addis Abeba.

Sowohl die Studie zu malignen Ovarialtumoren als auch die Vulvakarzinomstudie erhielten ein positives Ethikvotum vom Addis Ababa University Medical Faculty Institutional Review Board und von der Ethikkommission der Martin-Luther-Universität Halle-Wittenberg.

2. **Diskussion**

Im folgenden Teil werde ich die zentralen Ergebnisse der in dieser Dissertation eingeschlossenen Studien vorstellen. Diese Ergebnisse zeigen den Stand der Versorgung von Patientinnen mit malignen Ovarialtumoren und von Patientinnen mit Vulvakarzinom in Addis Abeba, Äthiopien, im Untersuchungszeitraum. Sie sollen dazu beitragen, die Situation in Äthiopien im internationalen Vergleich einordnen zu können und Daten für das Ziel

der weltweiten Bekämpfung von Krebserkrankungen zur Verfügung zu stellen. Im darauffolgenden Abschnitt werden die Stärken und Limitationen dieser Arbeit erläutert, um daraus abgeleitete Erkenntnisse bei zukünftigen Forschungsarbeiten in die Studiengestaltung implementieren zu können. Abschließend fasst dieses Kapitel die Haupterkenntnisse zusammen und gibt Empfehlungen, wie die Versorgung von Patientinnen mit malignen Ovarialtumoren bzw. mit Vulvakarzinom verbessert werden könnte.

Dazu werde ich die Ergebnisse der einzelnen Studien diskutieren und jeweils mit Studien vergleichen, die in anderen Ländern durchgeführt wurden. Zuerst werde ich die Studie zu Patientinnen mit malignen Ovarialtumoren als Hauptthema dieser Dissertation vorstellen. Im Anschluss beschreibe ich die Studie zu Patientinnen mit Vulvakarzinom. Diese Ausführungen sollen dazu beitragen, die unzureichende Versorgungslage von Patientinnen mit gynäkologischen Tumoren in Äthiopien zum Untersuchungszeitpunkt aufzuzeigen. Zusammenfassend unterstreicht die Analyse der Studien die Notwendigkeit, den Zugang zu adäquater onkologischer Diagnostik und Therapie in Äthiopien zu verbessern.

2.1 Klinische Charakteristika und Überleben von Patientinnen mit malignen Ovarialtumoren in Addis Abeba

In dieser Studie wurden sowohl klinische Daten von Patientinnen mit malignen Ovarialtumoren als auch populationsbezogene Daten aus dem Addis Ababa City Cancer Registry untersucht. Das mediane Alter von 47 Jahren in beiden Gruppen war, im Vergleich zu Daten aus den USA (63 Jahre) und Deutschland (69 Jahre), niedrig [18,19]. Dies lässt sich unter anderem durch den hohen Anteil von Keimzell- und Keimstrang-Stroma-Tumoren, welche typischerweise häufiger bei jungen Frauen auftreten, begründen. In der Gruppe der Patientinnen mit epithelialen Tumoren betrug das mediane Alter ebenfalls 47 Jahre, was durch die junge Bevölkerungsstruktur in Äthiopien erklärbar ist. In der Gesamtkohorte zeigten mehr als 25 % der Patientinnen nicht-epitheliale Tumore, wohingegen dieser Anteil im weltweiten Vergleich weniger als 10 % ausmacht [20].

Für die operierten Patientinnen mit epithelialen Ovarialtumoren wurden Hazard Ratios berechnet, die nach Alter, FIGO-Stadium, Therapie (nur Operation bzw. Operation und adjuvante Chemotherapie) und postoperativem Residualtumor adjustiert wurden. Die Diagnosen wurden meist in fortgeschrittenen Stadien gestellt; 75 % der Patientinnen befanden sich in FIGO Stadium II oder höher. Diese Zahl lässt eine unzureichende Diagnostik und, darauf basierend, eine zu niedrige Einordnung der Patientinnen vermuten. Im weltweiten

Vergleich werden mehr als 75 % der Patientinnen in FIGO Stadium III oder höher diagnostiziert (Deutschland: 76 %)[18]. Patientinnen in höheren Stadien hatten ein höheres Risiko zu versterben (FIGO III: HR= 2.91; 95 % KI= 0.67–12.64; FIGO IV: HR= 3.03; 95 % KI= 0.69–15.79).

Obwohl die vollständige operative Entfernung der wichtigste prognostische Faktor für das Überleben ist, wurden in dieser Kohorte nur 82 % der Patientinnen operiert [21]. Bei 50 % der Patientinnen zeigte sich postoperativ ein Residualtumor, der das Risiko zu versterben erhöhte (HR= 2.23). Daher sollte für die Patientinnen der Zugang zu optimaler operativer Therapie verbessert werden. Dies stimmt mit der grundsätzlichen Empfehlung zur bestmöglichen operativen Therapie beim Ovarialkarzinom überein [22]. Dieses Ergebnis ist kongruent mit Daten aus anderen Studien, in denen deutlich die Benachteiligung von Patientinnen und Patienten in Ländern mit niedrigem Einkommen aufgrund des limitierten Zugangs zu chirurgischer Therapie beschrieben wird [23-25]. Im Jahr 2013 praktizierten nur vier ausgebildete gynäkologische Onkologen in Äthiopien. Für eine verbesserte operative Versorgung werden dringend mehr gynäkologische OnkologInnen benötigt [26].

Da für Patientinnen mit FIGO-Stadium >IA eine platin-basierte adjuvante Chemotherapie empfohlen wird, in dieser Kohorte (alle Patientinnen FIGO-Stadium >IA) jedoch nur 59 % eine Chemotherapie erhielten, sollte der Zugang zu Chemotherapeutika ausgebaut werden [21]. Entgegen der Empfehlung zur adäquaten Schmerztherapie in der leitliniengerechten Behandlung von Ovarialkarzinomen erhielten trotz fortgeschrittener Stadien nur 29 % der Patientinnen eine Schmerzmedikation, was deutlich die Notwendigkeit der Verbesserung der Palliativ- und Schmerztherapie zeigt [21].

Die geschätzte 5-Jahres-Überlebensrate der klinischen Patientinnen (alle histologischen Subtypen) lag bei 33.9 %. Da eine Klassifikation der histologischen Subtypen in Äthiopien oft nicht verfügbar ist, wurden die geschätzte 5-Jahres-Überlebensrate für alle Patientinnen mit malignen Ovarialtumoren gemeinsam bestimmt. Das Ergebnis ist vergleichbar mit anderen Daten aus der Region (Sudan 38 %) [27], jedoch schlechter im Vergleich zu Daten aus Westeuropa (Deutschland 41 %) [18]. Die populationsbezogenen Registerpatientinnen zeigten 1- bzw. 2-Jahres-Überlebensraten von 73.9 % bzw. 51,8 %, ebenfalls geringer als eine populationsbezogene Kohorte aus den USA (78.3 % bzw. 66.8 %) [19]. Trotz der limitierten Therapieoptionen zeigten sich die Überlebensraten höher als erwartet, was sich durch die vergleichsweise hohe Anzahl von Tumoren mit besserer Prognose (Keimzell-, Keimstrang-Stroma- und Borderline-Tumore) erklären lassen könnte. Die insgesamt niedrigen

Überlebensraten zeigen, dass der schnelle Zugang zu operativer Therapie, Chemotherapie und palliativer sowie Schmerztherapie verbessert werden muss [15].

Bei diesem Projekt und der Veröffentlichung war ich hauptverantwortlich für die Erstellung des Studiendesigns sowie für die Planung der organisatorischen Umsetzung. Im Dialog mit den Ärzten des Black Lion Hospitals und des Zewditu Memorial Hospitals sowie den Mitarbeitern des Krebsregisters habe ich ein Konzept für die Gestaltung und Durchführung der Studie erstellt. Während eines viermonatigen Aufenthaltes in Addis Abeba, Äthiopien, habe ich die klinischen und die Krebsregisterdaten erhoben. Die Daten habe ich im Anschluss qualitätsgesichert und ausgewertet. Die Ergebnisse habe ich mit den beteiligten Kollegen und Kolleginnen diskutiert. Dafür habe ich eine Literaturrecherche zu klinischen Charakteristika und Überleben von Patientinnen mit malignen Ovarialtumoren durchgeführt und dabei einen besonderen Fokus auf Literatur aus Afrika gelegt. Meine Aufgabe war die Erstellung von Tabellen und Grafiken und die Verfassung des Manuskriptes für die Veröffentlichung mit Unterstützung durch die Kommentare und Anmerkungen der Ko-Autoren. Abschließend war ich für die Einreichung der Publikation bei internationalen Fachzeitschriften und die Begleitung des Prozesses bis zum Abschluss der Veröffentlichung verantwortlich.

2.2 Überleben von Patientinnen mit Vulvakarzinom in Addis Abeba

Für diese Studie wurden klinische Daten von 86 Patientinnen mit Vulvakarzinom ausgewertet. Das mediane Alter bei Diagnose war mit 38 Jahren im Vergleich zu Daten aus den USA (68 Jahre) niedrig, was sich vor allem auf die junge Bevölkerungsstruktur in Äthiopien zurückführen lässt [19].

Obwohl die HIV-Prävalenz in Äthiopien sehr niedrig ist (2014: 1.14 %), waren 57 % der Patientinnen mit Vulvakarzinom in dieser Kohorte HIV-positiv [28]. Ähnliche Ergebnisse wurden in einer südafrikanischen Studie beschrieben, in der 50 % (2014) bzw. 41 % (2015) der Vulvakarzinom-patientinnen HIV-positiv waren [13]. Dies unterstreicht die Notwendigkeit sowohl der HIV-Testung bei Vulvakarzinompatientinnen als auch, wie bereits grundsätzlich in den Empfehlungen zum Krebsscreening für HIV-Erkrankte empfohlen, das Screening auf Vulvakarzinom bei HIV-positiven Patientinnen [29]. Sowohl eine HIV-Infektion als auch junges Lebensalter sind Risikofaktoren für das HPV-assoziierte Vulvakarzinom [13,30]. Bisher finden in Äthiopien bei Vulvakarzinompatientinnen keine Tests für HPV statt, sodass dazu keine Datenlage generiert werden konnte.

Die 1-Jahres-Überlebensrate war mit 80 % vergleichbar mit der Überlebensrate von Patientinnen aus England (83 %). Die 2-Jahres-Überlebensrate sank bei den äthiopischen Patientinnen jedoch bereits auf 51 %, wohingegen in der englischen Kohorte die 5-Jahres-Überlebensrate noch 69.9 % betrug [10]. Dies lässt sich durch die späte Diagnosestellung und die unzureichenden Therapiemöglichkeiten in Äthiopien begründen. Die Patientinnen, die eine Therapie erhalten haben, zeigten längere Überlebenszeiten (Strahlentherapie: HR= 0.36; 95 % CI= 0.14–0.90; Operation: HR= 0.44; 95 % CI= 0.19–1.03; Chemotherapie: HR= 0.42; 95 % CI= 0.15– 1.12) [16]. Diese Ergebnisse sind übereinstimmend mit den aktuellen Empfehlungen zur Therapie beim Vulvakarzinom und zeigen, dass der Zugang zu oben genannten Therapieformen in Äthiopien verbessert werden muss [31].

Diese Studie hat Herr Kröber federführend geleitet und publiziert. Im Rahmen dieser Veröffentlichung habe ich bei der Planung und Konzeption des Studiendesigns und der Studiendurchführung mitgewirkt. Während meines viermonatigen Aufenthaltes in Äthiopien haben wir gemeinsam Daten für die Studie erhoben und Qualitätssicherung der Daten durchgeführt. Im kollegialen Austausch war ich an der Datenanalyse und -interpretation sowie der Erstellung der Grafiken für die Präsentation der Ergebnisse beteiligt. Weiterhin habe ich an der Verfassung des Manuskriptes sowie dessen Überarbeitung durch Rückfragen und kritische Anmerkungen mitgewirkt.

2.3 Stärken und Limitationen

In den beiden Studien zu Patientinnen mit malignen Ovarialtumoren und Vulvakarzinomen wurden erstmals Daten größerer Kohorten aus Subsahara-Afrika gewonnen. Es war dabei möglich, populationsbezogene sowie detailliertere klinische Daten zu Charakteristika und Therapieinformationen zu gewinnen. Dadurch wurde eine Lücke in der bisherigen Literatur zu gynäkologischen Krebserkrankungen in Subsahara-Afrika geschlossen. Auf Basis der gewonnen Erkenntnisse konnten wissenschaftlich fundierte Handlungsempfehlungen zur Verbesserung der regionalen Gesundheitsversorgung formuliert werden. Beide Studien wiesen verschiedene Limitationen auf.

Eine Limitation der Studie zu malignen Ovarialtumoren lag in der Zusammensetzung der Gesamtkohorte aus populationsbezogenen und klinischen Daten, sodass ein direkter Vergleich mit anderen populationsbezogenen Daten nicht möglich war. Zum Zweiten war die Qualität der klinischen Daten limitiert, da die Patientenakten handgeschrieben und teilweise unvollständig waren. Aufgrund von Lücken in der OP-Dokumentation wurden die

prognostischen Faktoren für das Überleben von nur 125 gut dokumentierten, operierten Fällen analysiert. Drittens kamen 375 Patientinnen (77 %) aus Addis Abeba. Da 80 % der Bevölkerung Äthiopiens in ländlichen Gebieten lebt, repräsentierte die untersuchte Kohorte eine vergleichsweise kleine urbane Gruppe von Patientinnen mit besserem Zugang zu Gesundheitseinrichtungen, verglichen mit der Allgemeinbevölkerung. Eine vierte Limitation lag in der vermutlich hohen Anzahl nicht diagnostizierter, nicht erfasster Patientinnen aufgrund der eingeschränkten onkologischen Versorgungsmöglichkeiten in Äthiopien. Eingeschlossen wurden Patientinnen aus den Operationsregistrationsbüchern bzw. mit klinisch deutlicher Symptomatik (klinische Patientinnen) sowie Patientinnen mit histologisch gesicherter Diagnose (Registerpatientinnen). Nicht-operierte sowie Patientinnen ohne typische Symptome wurden wahrscheinlich nicht an eine onkologische Einrichtung überwiesen.

Eine Limitation in der Vulvakarzinomstudie war das Fehlen von detaillierten Informationen bei 35 der 86 Patientinnen, sodass nur teilweise Daten zum HIV-Status und Lymphknotenstatus erhoben werden konnten. Zweitens war es nicht möglich, Patientinnen aus der chirurgischen Abteilung des Black Lion Hospitals einzuschließen, sodass Fälle, die ausschließlich operativ behandelt wurden, in dieser Kohorte möglicherweise unterrepräsentiert sind. Zum Dritten war eine Einteilung der Vulvakarzinome in HPV-assoziiert und Nicht-HPV-assoziiert nicht möglich, da eine Testung in Äthiopien nicht verfügbar war. Viertens zeigten sich die Informationen zum Todeszeitpunkt der Patientinnen, die von den Angehörigen der Patientinnen erfragt wurden, teilweise ungenau, sodass eine genaue Überlebenszeit teilweise nicht ermittelt werden konnte. Hier traten vermutlich Abweichungen in beide zeitlichen Richtungen auf und ergaben eine daher vernachlässigbare Verzerrung der Gesamtergebnisse.

2.4 Zusammenfassung und Ausblick

Maligne Ovarialtumore machen einen relevanten Anteil der Krebserkrankungen in Äthiopien aus. Sie treten bereits in frühem und mittlerem Lebensalter auf. Durch ihre lange Krankheitsdauer kommt es zu einer starken Belastung der Patientinnen und ihrer Familien. Im Gegensatz zu anderen gynäkologischen Tumoren gibt es für das Ovarialkarzinom keine effektiven Screening- oder Früherkennungsmethoden. Trotzdem bestehen Möglichkeiten auch mit geringen Ressourcen das Überleben und die Lebensqualität der Patientinnen zu verbessern. Insbesondere die in dieser Kohorte häufig vertretenen jungen Patientinnen mit nicht-epithelialen Tumoren profitieren von einer Therapieoptimierung. Durch Verbesserung der gynäko-onkologischen und operativen Ausbildung kann mehr Patientinnen der Zugang zu einer qualitativ hochwertigen Operation ermöglicht werden [32]. Wie auch in anderen Ländern

mit geringem Einkommen, sollte die Verfügbarkeit von Chemotherapie erhöht werden [33]. Speziell Patientinnen in fortgeschrittenen Stadien benötigen eine Ausweitung von Palliativmedizin und adäquater Schmerztherapie.

Das Vulvakarzinom ist in Äthiopien eine eher seltene Krebsentität, zeigt jedoch über die letzten Jahre steigende Inzidenzzahlen. Insbesondere junge Patientinnen sind häufig betroffen. Die hohe Rate an HIV-positiven Patientinnen mit Vulvakarzinom zeigt, dass HIV-positive Patientinnen gezielt im Hinblick auf ein mögliches Vulvakarzinom ein Screening erhalten sollten sowie Patientinnen mit diagnostiziertem Vulvakarzinom eine HIV-Testung erhalten sollten. Dieses Vorgehen würde eine bessere Therapieplanung ermöglichen sowie zur Vermeidung von Langzeitfolgen durch unerkannte bzw. in spätem Stadium erkannte Begleiterkrankungen beitragen. Die flächendeckende Einführung einer HPV-Testung in Äthiopien wäre ein weiterer Schritt, um eine genauere Diagnostik und Klassifizierung des Tumortyps zu ermöglichen sowie die Prävention weiter auszubauen. Für Patientinnen mit bestehendem Vulvakarzinom ist es essentiell, den Zugang zu operativer Therapie, Strahlentherapie und Chemotherapie zu verbessern. Patientinnen mit Tumoren in fortgeschrittenen Stadien sollten eine adäquate Palliativtherapie erhalten.

Für zukünftige Forschung ist von Interesse, inwieweit das Überleben und die Lebensqualität von Patientinnen mit malignen Ovarialtumoren sowie mit Vulvakarzinom verbessert werden konnten, da mittlerweile 15 ausgebildete Gynäko-Onkologen in Äthiopien praktizieren. Zusätzlich ist von Relevanz, inwieweit durch genauere pathologische und molekularbiologische Untersuchungen die Diagnostik und Therapieplanung optimiert werden können.

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Thesen

1. Das mediane Alter bei der Erstdiagnose betrug sowohl in der Gesamtkohorte als auch bei Patientinnen mit epithelialen Tumoren 47 Jahre, passend zu der jungen Bevölkerungsstruktur Äthiopiens. Wie erwartet bei jungen Patientinnen zeigten 25 % nicht-epitheliale Tumore.
2. Etwa 50 % der Patientinnen wurden zum Diagnosezeitpunkt als FIGO-Stadium I oder II klassifiziert, wesentlich mehr als in den USA oder Westeuropa. Die Stadien sind möglichweise zu niedrig und durch eingeschränkte Verfügbarkeit histologischer und laborchemischer Untersuchungen sowie fehlende Bildgebung erklärbar.
3. Trotz Indikation erhielten lediglich 82 % der Patientinnen eine operative Therapie und 59 % eine platin-basierte adjuvante Chemotherapie (beide Therapieoptionen führten zu einer höheren Überlebenswahrscheinlichkeit). Nur 29 % der Patientinnen erhielten eine supportive Therapie.
4. Bei postoperativem Residualtumor zeigte sich eine relevante Verschlechterung der Überlebenszeit (HR= 2.23; 95 % KI= 1.08–4.49).
5. Die geschätzten 1- und 2-Jahres-Überlebensraten der gesamten Kohorte betrugen 78,3 % und 59,2 %. Die geschätzte 5-Jahres-Überlebensrate betrug 33.9 %.
6. Die Verfügbarkeit gynäko-onkologischer Chirurgie und der Zugang zu Chemo- und Supportivtherapie sollte in Äthiopien erhöht werden, um die Überlebenswahrscheinlichkeit und Lebensqualität von Patientinnen mit malignen Ovarialtumoren zu steigern.
7. Das mediane Alter bei Erstdiagnose von Vulvakarzinompatientinnen in Äthiopien lag bei 39 Jahren, was einen großen Anteil HPV-assoziierter Karzinome vermuten lässt. Mit 57 % waren deutlich mehr Patientinnen HIV-positiv als in der Allgemeinbevölkerung. Etwa 83 % der Patientinnen wurden im FIGO-Stadium 1-3 diagnostiziert.
8. Patientinnen, die eine der verfügbaren Therapiearten (Strahlentherapie (HR= 0,36; 95 % KI= 0,14; 0,90), Operation (HR= 0,44; 95 % KI= 0,19-1,03), Chemotherapie (HR= 0,42; 95 % KI= 0,15-1,12)) erhielten, zeigten tendenziell ein längeres Überleben.
9. Die geschätzte 1-Jahres-Überlebensrate der Vulvakarzinompatientinnen lag bei 80 %; nach zwei Jahren sank diese auf 51 %.
10. Insbesondere unter den jungen Patientinnen beider Kohorten ist eine sensible Aufklärung und adäquate Operation unter Berücksichtigung von Sexualität und Kinderwunsch erforderlich. Die Lebensqualität aller Patientinnen kann durch Zugang zu Palliativ- und Schmerztherapie erhöht werden.

Anlagen

Anlage A

Piszczan, S., Desalegn, D., Petros, H., Gurmu, M., Kroeber, E. S., Addissie, A., Mikolajczyk, R., Ghebre, R. G., Mathewos, A., Thomssen, C., Jemal, A., & Kantelhardt, E. J. (2019). Clinical Characteristics and Survival of Patients with Malignant Ovarian Tumors in Addis Ababa, Ethiopia. *The Oncologist*, *24*(6), e303–e311.

Anlage B

Kroeber, E. S., Mathewos, A., Wondemagegnehu, T., Aynalem, A., Gemechu, T., Piszczan, S., Timotewos, G., Addissie, A., Wienke, A., Unverzagt, S., Thomssen, C., Jemal, A., & Kantelhardt, E. J. (2018). Vulvar cancer in Ethiopia: A cohort study on the characteristics and survival of 86 patients. *Medicine*, *97*(9), e0041.

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Global Health and Cancer

Clinical Characteristics and Survival of Patients with Malignant Ovarian Tumors in Addis Ababa, Ethiopia

Swantje Piszczan,[a] Dawit Desalegn,[b] Hezkiel Petros,[b] Mengistu Gurmu,[b] Eric Sven Kroeber,[c] Adamu Addissie,[d] Rafael Mikolajczyk,[c] Rahel G. Ghebre,[e] Assefa Mathewos,[d] Christoph Thomssen,[a] Ahmedin Jemal,[f] Eva Johanna Kantelhardt[a]

[a]Department of Gynecology, Martin-Luther-University, Halle an der Saale, Germany; [b]Department of Gynecology and Obstetrics, Addis Ababa University, Ethiopia; [c]Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University, Halle an der Saale, Germany; [d]Radiotherapy Center, School of Medicine, Addis Ababa University, Ethiopia; [e]Department of Obstetrics, Gynecology and Women's Health, University of Minnesota, Minneapolis, Minnesota, USA; [f]American Cancer Society, Atlanta, Georgia, USA

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

Key Words. Ovarian neoplasms • Ovarian cancer • Survival • Africa • Ethiopia

Abstract

Background. Ovarian cancer is the third leading cause of cancer death among women in Ethiopia, with about 2,550 diagnosed cases and 2,000 deaths each year. The incidence and mortality rates of this disease have been increasing in Ethiopia and other parts of sub-Saharan Africa over the past decades because of changing lifestyle and reproductive factors. In this study, we describe the clinical characteristics, treatment patterns, and survival of patients with ovarian cancer in Ethiopia.

Materials and Methods. This retrospective cohort study included 485 patients diagnosed between January 2009 and October 2015 at Addis Ababa University Hospital, Zewditu Memorial Hospital, or registered in the Addis Ababa population-based cancer registry. Follow-up data were obtained via telephone. Primary endpoint was all-cause mortality.

Results. The median age was 46 years (range, 11–95). The estimated 1- and 2-year overall survival rates were 78% (95% confidence interval [CI] 0.741–0.82.5) and 59% (95% CI, 0.538–0.646), respectively. Of those patients with result available (n = 423), 73.0% had epithelial cancers. Almost half were classified as Federation of Gynecology and Oncology stage III or IV (48.2%; stage available n = 201) resulting in worse outcomes (hazard ratio [HR], 2.91 [CI 0.67–12.64] and 3.03 [0.69–15.79], respectively). Four out of five patients received some form of surgery (82%), three out of five received platinum-containing chemotherapy. Patients with residual tumor after surgery (n = 83) showed worse survival outcome (HR, 2.23; 95% CI 1.08–4.49).

Conclusion. Our study revealed substantial treatment gaps with respect to surgery and adequate chemotherapy. Higher stage, residual tumor and lack of chemotherapy impaired the outcome. Access to higher standards of ovarian cancer treatment is urgently needed in Ethiopia. ***The Oncologist*** 2019;24:e303–e311

Implications for Practice: Ovarian cancer is often a fatal disease in high resource settings; now it is also becoming important in Ethiopia. This study included 485 women with malignant ovarian tumors treated in Addis Ababa who had a mean age of only 46 years because of the young population structure. Three quarters had the typical epithelial cancer, with half presenting with advanced stage III and IV. Improved oncologic surgery and sufficient chemotherapy could possibly improve their outcome. The relatively high proportion of women with nonepithelial cancer need adequate treatment options to have good prognosis.

Introduction

Ovarian cancer (OC) is the seventh most common cancer diagnosis and the eighth leading cause of cancer death in women worldwide, with 238,719 cases and 151,917 cancer deaths in 2012. Incidence rates vary geographically, with the highest rates reported from Northern America and Europe and the lowest from Africa and South America. Over the past decade incidence rates have increased in low- and middle-income countries. In sub-Saharan Africa and Ethiopia, OC is the third most common diagnosed cancer among women, with an estimated number of 12,705 and 2,550 cases in 2012, respectively [1–5].

Correspondence: Eva Johanna Kantelhardt, M.D., Department of Gynecology, Martin-Luther-University, Ernst-Grube-Str. 40, 06097 Halle, Germany. Telephone: 49-345-557-1847; e-mail: Eva.kantelhardt@uk-halle.de Received December 11, 2018; accepted for publication March 18, 2019; published Online First on April 25, 2019. http://dx.doi.org/10.1634/theoncologist.2018-0869

Studies suggest that there are high incidence rates of OC in countries with high development index (HDI); similarly HDI countries demonstrate higher prevalence of known OC risk factors including nulliparity/low parity, advanced age, hormone replacement therapy and family predisposition [6]. Increasing life expectancy and a more westernized lifestyle has led to rising numbers in countries with a low development index (LDI) [7, 8]. The above-mentioned risk factors are associated with epithelial tumors, which account for 90% of all ovarian cancers [9]. The remaining nonepithelial tumors include germ cell and sex cord-stromal tumors [10]. Risk factors, treatment, and prognosis vary greatly depending on the histologic subtype [11]. Borderline ovarian tumors behave like malignant tumors but in in less aggressive fashion with significantly better outcome over malignant ovarian tumors [12, 13]

Even in high-income countries, OC has poor prognosis [5]. The 5-year survival rate for OC is between 30%–41% [2, 11]. The absence of effective screening methods complicates early detection [14]. Survival is mainly effected by the extent of disease spread at diagnosis, reflected in the Federation of Gynecology and Oncology (FIGO) stage; access to adequate oncologic surgery, because optimal surgery with tumor free postoperative status is an important prognostic factor [15]; and the delivery of adequate platinum-taxane-based combination chemotherapy. Because of the poor prognosis of OC, palliative care and pain management are important aspects of OC therapy [16].

Ethiopia is the second most populous country in sub-Saharan Africa, with an estimated 102 million population in 2016 and more than 51 million women [17]. With approximately 80% of the population living in rural areas, Ethiopia is one of the least urbanized countries in the world [17, 18]. Generally, delay in diagnosis contributes to large proportion of OC in sub-Saharan African presenting in advanced stages of cancer, thus impairing outcome [8]. Low access to adequate medical care specialized for cancer treatment additionally negatively affects the outcome of patients with OC [19]. In 2013, only four gynecologic oncologists were performing surgeries on OC in Ethiopia [20]. Access to chemotherapy and palliative care is a challenge to oncology care in Ethiopia and other parts of Africa, compounded by the rising cancer burden [21]. In Ethiopia, 90% of all patients with cancer report problems accessing palliative care services [22].

The rising burden of ovarian tumors in Ethiopia is prospectively captured in a population-based cancer registry of Addis Ababa, Ethiopia [23]. The Addis Ababa City Cancer Registry (AACCR) registered patients reported from Addis Ababa health facilities with histological verification or strong clinical evidence from 19 centers in town, including pathology centers, oncology clinics, the main referral hospitals, and diagnostic facilities. The objective of our study was to evaluate clinical and pathological characteristics, along with therapy provided including pain and palliative care management, and overall survival of patients with ovarian malignancies (OM) of all histologic types. This analysis included patients treated at two major referral hospitals and the population-based cancer registry of Addis Ababa, Ethiopia. Because palliative care was not well developed in Ethiopia, special focus was given to ascertain information about symptoms and therapy received. This is the first study to report on the current pattern of ovarian malignancies and treatment outcome in referral hospitals in Ethiopia.

Materials and Methods

Patient Selection

We used data from consecutive patients treated from 2009–2015 in hospitals and a population-based cohort from 2011–2015 with malignant ovarian tumors to construct a retrospective cohort. We included women who were treated at the Department of Gynecology and the Oncology Center at Black Lion Hospital (BLH) Addis Ababa University and the Department of Gynecology at Zewditu Memorial Hospital (ZMH; referred to as "clinical patients"). The population-based cohort included patients registered in the AACCR (referred to as "registry patients") (Fig. 1). The AAACR cohort includes Addis Ababa residents from 19 centers in Addis Ababa city including BLH and ZMH hospital registry. In total, 263 registry patients were captured through the registry but additional clinical information was not traced. A total of 86 clinical patients were captured in both, 100 clinical patients were captured with diagnosis before start of the registry, and 36 clinical patients with files retrieved but missed by population-based registration. Patients are included into AAACR registry with histologic verification. We found no difference between the characteristics of the two groups and decided to analyze them together resulting in a cohort of 485 patients (total cohort) with OM in Addis Ababa region.

In BLH and ZMH, 683 patients received therapy for an ovarian abnormality; 222 of these patients with files available were diagnosed with malignant ovarian tumors between January 2009 and October 2015. Central review of histopathology was not possible; cases were processed according to standards of the ten local laboratories. For these clinical patients, patient characteristics, clinical information such as therapy, and outcome information were abstracted from patient files. Additionally, 349 patients with malignant ovarian tumors were registered in the AACCR between September 2011, when the cancer registry started, and October 2015. About half of the cases (n = 189, 54%) originated from BLH; the other participating hospitals registered 1–37 cases in this period. Of those 349 patients, 86 patients were duplicates in clinical cases from either BLH or ZMH registry, and those were merged. Finally, 263 cases were included in the study. For these registry patients, only data on the date of diagnosis, topology, and histology such as date of last contact was collected; no detailed information on clinical aspects or therapy was available.

Histologically verified diagnosis of an OM (International Classification of Disease for Oncology-O-3 codes C56.9) was available for 423 patients, and 5 patients had a positive cytology only. Tumor histology was grouped into epithelial tumor (n = 355), germ cell tumor (n = 40), sex cord-stromal tumor (n = 15), and borderline tumor (n = 13) using the World Health Organization classification of tumors of the ovary (updated version from 2013) [24]. Additionally, 57 patients were diagnosed based on strong clinical evidence without histological verification.

Follow-up information on survival status and date of last contact was collected via telephone contact with patients or

their relatives by trained staff of the AACCR. If a person could not be reached by telephone or the telephone number was missing, the last date recorded in the file was used as date of last contact (n = 126).

In 13 cases, the date of death given by the relatives was in contradiction to a later date of last contact in the file. Assuming the date in the file was reliable, date of death was assumed to be 3 months after the date of last contact in the file, because this was the time between regular follow-up visits.

Staging

Tumors were classified according to the International FIGO staging system [25]. Information on stage was extracted from surgical operative and pathology report. Patients without surgery were classified according to clinical findings and additional imaging such as chest x-ray, abdominal ultrasound, or computed tomography (CT) scan and, if performed, cytology of pleural effusion or ascites. In cases of distant metastases mentioned in chest x-ray, abdominal ultrasound, or CT scan, the stage was classified as IVB.

Treatment modalities

Characteristics of treatment were described for patients with information available. For clinical patients, information was taken from the patient clinical files. For registry patients, information from AACCR was supplemented by basic questions from the telephone interview about surgery and/or chemotherapy. For evaluation of survival, we included clinical patients with histologically verified epithelial tumors and who received an oncologic surgery (n = 125).

Surgeries reported included bilateral or unilateral salpingo-oophorectomy, abdominal hysterectomy, and omentectomy. Adjuvant chemotherapy was classified as cisplatinum/cyclophosphamide (6 cycles with 60–75 mg per m^2/650–900 mg per m^2), cisplatinum/paclitaxel (6 cycles with 60–75 mg per m^2/175 mg per m^2), carboplatin/paclitaxel (AUC-5 per $m^{2/}$175 mg per m^2), or cisplatinum only (doses unknown), according to international standard protocols. Information on the type of chemotherapy was missing in three cases. If the patient did not receive all six cycles of chemotherapy, therapy was considered as incomplete.

Statistical Analysis

The primary endpoint of the study analysis was overall survival. Person time was the time from the date of pathologic diagnosis or, if not available, from the date of first presentation to the hospital for this complaint (n = 51) to the date of last contact. The median follow-up time for the surviving patients was 21 months (range, 0.1–78.8). To estimate the adjusted and unadjusted hazard ratios and the corresponding 95% confidence intervals for prognostic factors, we used a multivariate cox proportional hazard regression model. We conducted analyses using statistical software SPSS (IBM, Armonk, NY).

Ethical approval was obtained from the Institutional Review Board of the College of Health Science Addis Ababa University and by the Ethiopian Public Health Research Institute.

Results

Patient Characteristics

The majority of patients originated from Addis Ababa (n = 375, 77%). The median age was 47 (range, 11–95), and mean number of pregnancies was three (range, 0–10). Data on contraceptive use and HIV status were rarely available; only 18 women indicated ever having used contraceptives (4%), and 10 women were known to be HIV positive (2.1%; Table 1). Epithelial tumor was the most common histology in the cohort (total n = 355, 73.0%; adenocarcinoma not otherwise specified [NOS] n = 184, serous n = 121, mucinous n = 41, endometroid n = 4, clear cell n = 2, transitional n = 2, carcinosarcoma n = 1). Second most common histology was germ cell tumor (total n = 40, 8.2%; immature teratomas, n = 24, dysgerminoma n = 5, choriocarcinoma n = 3, sarcoma n = 3, yolk sac tumor n = 2, germinoma n = 1, embryonal carcinoma n = 1, mixed germ cell tumor n = 1). Third most common type was sex cord-stromal tumor (total n = 15, 3.0%; of those granulosa cell tumor n = 11, signet ring stroma tumor n = 4). Borderline tumors were the least common (total n = 13, 2.7%; borderline serous n = 12, borderline mucinous n = 1). Information on histology was missing for 62 cases (13.0%).

Of the clinical patients with detailed information from patient files available (n = 222), the majority presented with late symptoms, and very few were detected incidentally. We found abdominal swelling and abdominal pain as the most common symptoms. Further symptoms and signs included weight loss, palpable abdominal mass, and preoperative ascites. An elevated tumor marker cancer antigen (CA) 125 was found in about half the cases. Almost two thirds of the patients were classified as FIGO stage II or III, only 33 cases as FIGO stage I, and 40 cases as FIGO stage IV (Table 2).

Treatment Modalities

The majority of the patients received surgery (n = 400, 82%). Out of the clinical patients (all histologic types) with detailed surgical information (n = 222), bilateral salpingo-oophorectomy was frequently performed (n = 146, 55.3%), 28 patients received unilateral salpingo-oophorectomy (10.6%), hysterectomy was performed in 154 cases (58.3%), and omentectomy was performed in 106 cases (40.2%). A total of 283 patients received chemotherapy (59%). Most of the clinical patients were treated with cisplatinum and cyclophosphamide (n = 54, 19.0%), 38 were treated with cisplatinum and paclitaxel (13.4%), 16 received carboplatin and paclitaxel (5.6%), and 16 other patients varied chemotherapeutics agents (5.6%). The type of chemotherapy was unknown in 160 cases (56.3%). Pain medication was given to 64 patients (29%) only (Table 3).

Survival

During follow-up of the total cohort (n = 485), 190 patients died (39.3%). The overall 1-year survival rate was 78.3% (95% CI, 0.741–0.82.5), and the 2-year survival rate 59.2% (95% CI, 0.538–0.646; Fig. 2). The median survival time was 32.5 (estimate + uncertainty) months. The clinical patients showed a higher overall 1-year survival rate of 82.7% (95% CI, 0.773–0.881) compared with the population-based registry patients (73.9%; 95% CI, 0.677–0.801); the 2-year survival

Table 1. Socio-demographic and reproductive patient characteristics of the total cohort (n = 485)

Patient characteristics	Total, count (%)	Histologic subtype of tumor, count (%)				
		Epithelial, 84.0%[a]	Germ cell, 9.4%[a]	Sex cord-stromal, 3.5%[a]	Borderline, 3.1%[a]	Cyto only/ no patho
Total	485	355	40	15	13	62
Origin						
Addis Ababa	375 (77)	294 (83)	33 (83)	10 (67)	7 (54)	31 (50)
Not Addis Ababa	100 (21)	56 (16)	5 (13)	5 (33)	5 (38)	29 (47)
Unknown	10 (2)	5 (1)	2 (5)		1 (8)	2 (3)
Age						
<30	60 (12)	41 (12)	8 (20)	3 (20)	1 (8)	7 (11)
30–39	106 (22)	83 (23)	7 (18)	4 (27)	4 (31)	8 (13)
40–49	109 (23)	78 (22)	5 (13)	3 (20)	4 (31)	19 (31)
50–59	102 (21)	73 (21)	8 (20)	4 (27)	1 (8)	16 (26)
60–69	60 (12)	47 (13)	5 (13)		2 (15)	6 (10)
>70	42 (9)	28 (8)	6 (15)	1 (7)	1 (8)	6 (10)
Unknown	6 (1)	5 (1)	1 (3)			
Age, median (range)		47 (11–95)	47 (12–77)	42 (16–82)	48 (25–76)	48 (14–72)
Parity						
0–1	73 (15)	37 (10)	7 (18)	4 (27)	8 (62)	17 (27)
2–3	49 (10)	29 (8)	2 (5)	1 (7)	3 (23)	14 (23)
>4	70 (14)	36 (10)	4 (10)	1 (7)	2 (15)	27 (44)
Unknown	293 (61)	253 (71)	27 (68)	9 (60)		4 (6)
Usage of contraceptives						
Yes	18 (4)	10 (3)			1 (8)	7 (11)
No	85 (17)	41 (12)	5 (13)	5 (33)	6 (46)	27 (44)
Unknown	382 (79)	304 (86)	35 (88)	10 (67)	6 (46)	28 (45)
HIV status						
Positive	10 (2)	3 (1)	3 (8)	1 (7)	1 (8)	2 (3)
Negative	7 (1)	5 (1)				2 (3)
Unknown	468 (97)	347 (98)	37 (93)	14 (93)	12 (92)	58 (94)

[a]Cases with known histologies.
Abbreviations: Cyto, cytology; patho, pathology.

rate was 66.3% (95% CI, 0.591–0.735) in clinical patients and 51.8% (95% CI, 0.438–0598) in registry patients (Fig. 3).

We tested whether assumed prognostic factors were associated with survival in patients with operated epithelial tumors: age, FIGO stage, addition of chemotherapy to surgery, and presence of residual disease. The outcome of patients receiving surgery without chemotherapy was similar compared with patients receiving combined surgery and chemotherapy (HR, 1.07; 95% CI, 0.54–2.11). The presence of a residual tumor after surgery was associated with a worse survival (HR, 2.23; 95% CI, 1.08–4.49, Table 4). Interestingly, age and stage were not significantly associated with the outcome considering the limited power of the assembled cohort.

Discussion

Our study is the first to present clinical characteristics and survival of patients with malignant ovarian tumors in Ethiopia. The overall 1-year and 2-year survival rates in this selected cohort from hospital and population-based cases were 78% and 59%, respectively. Most patients were diagnosed with epithelial type of ovarian cancer and presented with stage 3 disease. A majority of the patients received some form of surgery, but only two thirds received adjuvant chemotherapy. For patients with epithelial tumors, residual tumor after surgery was the most important prognostic factor for adverse outcome. A trend of worse outcome for higher stage was seen.

Patient Characteristics: Age Distribution

The median age in this study was 47 years (in all patients and in patients with epithelial tumors only). In high-income countries the average age at diagnosis is comparatively higher, (e.g., in the U.S., 63 years; in Germany, 69 years) [2, 26]. Reports from other sub-Saharan countries also show lower median ages, such as 45 years in Ghana, 52 years in Nigeria, and 49 years in Senegal [27–29]. The low median age in our patient cohort is attributable to the population structure in Ethiopia, where more than half of the population is younger than 20 years. It also reflects the higher proportion of germ cell and sex cord-stromal tumors in this cohort population,

Table 2. Clinical and pathological characteristics of the clinical patients (*n* = 222)

Clinical information	Total, count (%)	Histologic subtype of tumor, count (%)				
		Epithelial	Germ cell	Sex cord-stromal	Borderline	Cyto only/no patho
Total	222	127	13	7	13	62
Abdominal swelling						
Yes	160 (72)	81 (64)	11 (85)	5 (72)	12 (92)	51 (82)
No	24 (11)	14 (11)	2 (15)	1 (14)		7 (11)
Unknown	38 (17)	32 (25)		1 (14)	1 (8)	4 (6)
Abdominal distension/pain						
Yes	181 (82)	96 (75)	12 (92)	5 (72)	11 (85)	57 (92)
No	9 (4)	6 (5)	1 (8)	1 (14)		1 (2)
Unknown	32 (14)	25 (20)		1 (14)	2 (15)	4 (6)
Vaginal bleeding						
Yes	32 (14)	19 (15)		3 (43)		10 (16)
No	143 (64)	71 (56)	12 (92)	4 (57)	11 (85)	45 (73)
Unknown	47 (22)	37 (29)	1 (8)		2 (15)	7 (11)
Weight loss						
Yes	108 (49)	59 (46)	7 (54)	2 (29)	6 (46)	34 (54)
No	39 (17)	15 (12)	3 (23)	3 (42)	4 (31)	14 (23)
Unknown	75 (34)	53 (42)	3 (23)	2 (29)	3 (23)	14 (23)
Mass palpable						
Yes	126 (57)	61 (48)	9 (70)	3 (43)	10 (77)	43 (69)
Distended abdomen	36 (16)	19 (15)	2 (15)	2 (29)	2 (15)	11 (18)
No	54 (24)	42 (33)	2 (15)	1 (14)	1 (8)	8 (13)
Unknown	6 (3)	5 (4)		1 (14)		
Preoperative ascites						
Yes	79 (36)	40 (31)	3 (23)	3 (43)	4 (31)	29 (47)
No	65 (29)	26 (20)	6 (46)	3 (43)	4 (31)	26 (42)
Unknown	78 (35)	61 (48)	4 (31)	1 (14)	5 (38)	7 (11)
CA125 elevated						
Yes	120 (54)	77 (61)	4 (31)	3 (43)	11 (84)	25 (40)
No	51 (23)	17 (13)	4 (31)	3 (43)	1 (8)	26 (42)
Unknown	51 (23)	33 (26)	5 (38)	1 (14)	1 (8)	11 (18)
FIGO stage						
I	33 (15)	11 (9)	3 (23)	1 (14)	2 (15)	16 (26)
II	61 (27)	31 (25)	3 (23)	3 (43)	5 (38)	19 (31)
III	67 (30)	46 (36)	4 (31)	2 (29)	3 (23)	12 (19)
IV	40 (18)	22 (17)	3 (23)	1 (14)	2 (15)	12 (19)
Unknown	21 (10)	17 (13)			1 (8)	3 (5)

Clinical patients from two main referral hospitals in Addis Ababa.
Abbreviations: CA125, cancer antigen 125; cyto, cytology; FIGO, International Federation of Gynecology and Obstetrics; patho; pathology.

typically diagnosed in younger women. Data from Germany showed 27% of patients with OC with a mutation in at least one risk gene; 21% were BRCA 1–2 positive [30]. The low median age in our cohort may also suggest a high rate of genetic mutations; genetic testing or family history was not available. Long-term effects of cytoreductive surgeries as well as short and long-term toxicities from chemotherapy need to be considered in these young patients, highlighting the importance of cancer survivorship. An increase of ovarian cancer cases can also be expected because life expectancy is rising in Ethiopia (50 to 67 years between 1995–2015) [17].

Treatment modalities

In our cohort, 82% of all patients received surgery. Generally, the prognosis of ovarian malignancies and especially epithelial ovarian cancer is poor, especially in countries with low access to optimal treatment [31]. Surgery is a critical component of malignant ovarian tumor management, and all patients need access to surgical therapy [15]. We were unable to describe surgical procedures in detail in this retrospective study, but from 166 conclusive surgical notes we found 50% reporting residual disease. This shows the limited availability of optimal surgery. This is most likely due to

Table 3. Characteristics of first medical care, treatment and surgery results

Therapy information	Histologic subtype of tumor, count (%)					
	Total	Epithelial	Germ cell	Sex cord-stromal	Borderline	Cyto only/ no patho
First health facility (*n* = 222 clinical patients)						
Health center	44 (20)	19 (15)	1 (8)	1 (14)	5 (38)	18 (29)
Hospital	153 (69)	89 (70)	8 (61)	6 (86)	7 (54)	43 (69)
Referral hospital	16 (7)	13 (10)	3 (23)			
Unknown	9 (4)	6 (5)	1 (8)		1 (8)	1 (2)
Surgery received (*n* = 485 total cohort)						
Yes	400 (82)	283 (79)	35 (88)	12 (80)	13 (100)	57 (92)
No	85 (18)	72 (20)	5 (13)	3 (20)		5 (8)
Residual tumor (*n* = 215 operated patients among clinical patients)						
Yes	83 (39)	51 (41)	4 (31)	1 (14)	5 (38)	22 (39)
No	83 (39)	32 (26)	7 (54)	4 (57)	8 (62)	32 (56)
Unknown	49 (22)	42 (33)	2 (15)	2 (29)		3 (5)
Chemotherapy received (*n* = 485 total cohort)						
Yes	283 (59)	238 (67)	21 (53)	8 (53)	5 (38)	11 (18)
No	176 (36)	101 (28)	17 (43)	6 (40)	7 (54)	45 (72)
Unknown	26 (5)	16 (5)	2 (5)	1 (7)	1 (8)	6 (10)
Chemotherapy completed (*n* = 222 clinical patients)						
Yes	173 (78)	90 (71)	10 (77)	6 (86)	10 (77)	57 (92)
No	49 (22)	37 (29)	3 (23)	1 (14)	3 (23)	5 (8)
Pain medication received (*n* = 222 clinical patients)						
Yes	64 (29)	42 (33)	5 (38)	1 (14)	1 (8)	15 (24)
No	158 (71)	85 (67)	8 (62)	6 (86)	12 (92)	47 (76)

Clinical patients from two main referral hospitals in Addis Ababa.
Abbreviations: cyto, cytology; patho, pathology

Table 4. Unadjusted and adjusted hazard ratios for adverse outcome (death) of operated patients with epithelial ovarian cancers (*n* = 125)

Characteristic	Unadjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
Age <40[a]				
40–59	1.02 (0.58–1.80)	.948	1.14 (0.64–2.04)	.657
≥60	1.48 (0.66–3.33)	.346	1.25 (0.52–3.00)	.612
FIGO stage 1[a]				
Stage 2	1.80 (0.41–7.92)	.439	1.89 (0.43–8.35)	.400
Stage 3	3.37 (0.79–14.34)	.101	2.91 (0.67–12.64)	.154
Stage 4	3.81 (0.83–17.42)	.085	3.03 (0.69–15.79)	.134
Unknown	2.00 (0.41–9.74)	.388	2.16 (0.44–10.65)	.344
Surgery + CT[a]				
Surgery	1.05 (0.55–1.97)	.887	1.07 (0.54–2.11)	.849
No residual tumor[a]				
Residual tumor	2.45 (1.25–4.83)	.009	2.23 (1.08–4.49)	.025
Unknown	1.09 (0.51–2.33)	.825	1.16 (0.52–2.56)	.714

Adjusted for treatment, age, FIGO stage, residual tumor.
[a]Reference category.
Abbreviations: CI, confidence interval; CT, chemotherapy; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio.

the very small number of well-trained oncologic surgeons and thus ovarian surgery is being performed by non-specialized surgeons, which has been shown to result in reduced optimal surgical outcomes [32]. In 2013, only four gynecologic oncologists trained to perform surgeries on malignant ovarian tumors practiced in Ethiopia, a small

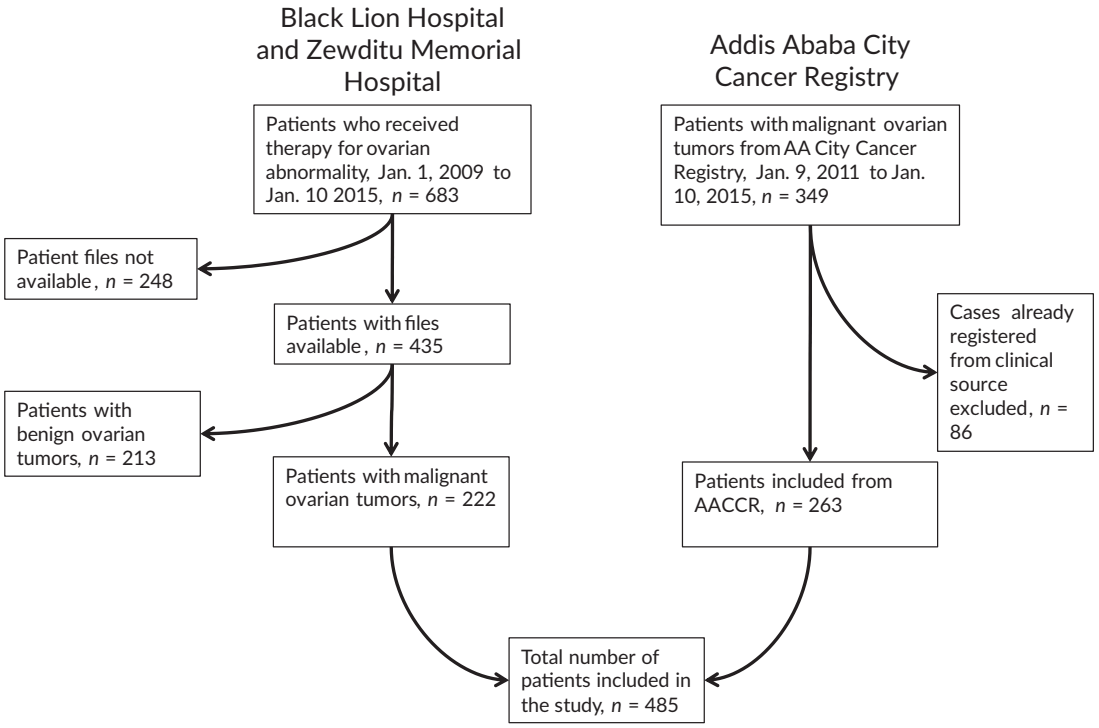

Figure 1. STROBE diagram. Patients included in the study were either diagnosed in Black Lion Hospital or Zewditu Memorial Hospital or registered in the AACCR.
Abbreviation: AACCR, Addis Ababa City Cancer Registry.

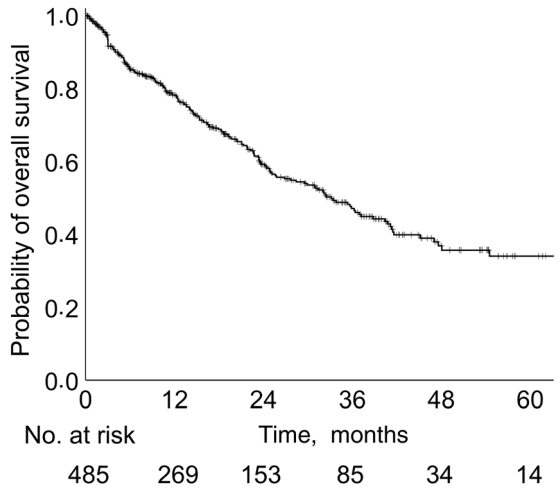

Figure 2. Estimated cumulative overall survival of the total cohort (*n* = 485; Kaplan-Meier method), hospital-based, and population-based data combined, all histologic subtypes included.

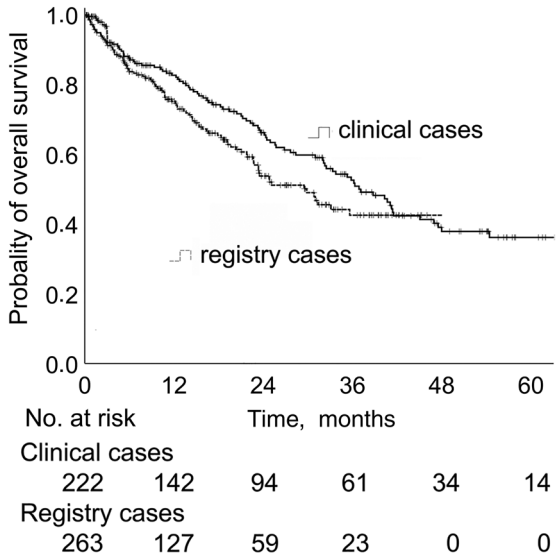

Figure 3. Estimated cumulative overall survival for clinical patients (*n* = 222) and registry patients (*n* = 263), mutually exclusive, all histologic subtypes included (Kaplan-Meier method).

number in relation to the 2,550 estimated yearly cancer cases in the whole country [20]. Furthermore, only three hospitals were equipped to perform complex oncologic surgeries and anesthetic as well as intensive care was limited. This clearly calls for action to improve quality and quantity of surgical oncologic services in Ethiopia. Patients with epithelial ovarian cancer stages higher than FIGO stage IA should receive a platinum-based adjuvant chemotherapy [15]. Chemotherapy was provided to 59% of patients in this cohort (all patients greater than stage IA); possible challenges to chemotherapy delivery include limited access to chemotherapy centers and shortage of chemotherapy drugs. Of patients with information on chemotherapy cycles, only 78% completed their total dose. Information on type of chemotherapy was incomplete but from the data available only a few patients (19%) received a taxane. Lack of financial resources and chemotherapy availability have been documented as barriers to chemotherapy delivery in sub-Saharan Africa [20]. Only 29% of clinical patients

received pain medication, a much lower than anticipated need considering the high proportion of advanced-stage diseases diagnosed in Ethiopia. Increasing access to palliative care is a global oncology priority.

Survival

The cumulative estimated crude overall 1-year and 2-year survival rate of our clinical patients (all histologic types) was 82.7% and 66.3%, respectively. The estimated 5-year survival rate was 33.9% (95% CI, 30.2%–37.6%), which is comparable to published data from Sudan (38%) but higher compared with data from Senegal (13%) [29, 33]. Compared with population-based data from the U.S. with a 1-year and 2-year survival rate of 78.3% and 66.8%, respectively, in 2012, our population-based registry patients had worse outcome (of 73.9% and 51.8%) but not as huge of a difference as possibly expected given the limited therapy available [26]. This could be partly explained by the fact that our patient cohort included a larger proportion of good-prognosis patients improving the outcome, such as germ cell tumors, sex cord-stromal tumors, and a sample of borderline epithelial tumors. However, at the same time, the relatively poor survival despite those good-prognosis patients may reflect patients with aggressive cancer and suboptimal therapy including suboptimal surgery, complete lack of surgery, or lack of standardized adjuvant chemotherapy. In addition, delay in diagnosis and long waiting times for surgery and chemotherapy contributes to disease progression and poor prognosis. Similar to other studies in epithelial cancer, overall survival was better in patients without residual tumor [34]. We assume that in Ethiopia, survival of all OMs is likely lower than reported in this study, accounting for the limited access to ovarian cancer diagnostic and treatment center across Ethiopia; a great number of patients are underdiagnosed in the rural settings. Patients without surgery are less likely to be registered in either clinical or population-based database and thus are not captured in this cohort.

Limitations

There are several limitations in this retrospective study. Firstly, the cohort is a mixture of population-based registered patients and patients with clinical records available. This does not allow comparison to studies reporting population-based data. All proportions described should be interpreted more behind the background of a selected hospital cohort. Second, the data quality was limited by the fact that patient files were handwritten and stored manually, and documentation was partly incomplete. Particularly, the operation notes were incomplete,and detailed information on size and position of residual tumors could not be gathered. Therefore, we only included $n = 125$ well-documented surgical cases in the assessment of prognostic factors on survival. Third, our cohort included 375 patients (77%) originating from Addis Ababa. As 80% of Ethiopia's population lives in rural areas, our cohort represented mainly a selected group of urban patients with good health care access. Fourth, the patient cohort was mostly generated from clinical operation registration books (clinical patients) and histologically verified and strong clinical evidence for OM (registry patients). Patients who were not operated on and without strong clinical evidence would likely not be referred to any facility with oncologic service. Because oncologic diagnostic service is still very limited in Ethiopia, there are no options to retrieve those underdiagnosed patients; thus, our total cohort and proportions described have a selection bias toward those patients with typical symptoms and access to good diagnostic facilities.

Conclusion

In this study, we presented for the first time a large cohort of Ethiopian patients diagnosed with malignant ovarian tumors. Knowing that these patients all over the world share a fatal outcome, we see room for improvement in Ethiopia. These considerably young patients (median, 46 years) had nonepithelial tumors in nearly one third of cases; in this respect they were markedly different from European or U.S. settings and thus call for local guideline development. The 62 patients without histologic confirmation (34 below the age of 50) definitely need better health service given the relatively high possibility of having a treatable nonepithelial tumor. The common presentation at high tumor stage shows the lack of screening strategies similar to other countries. Of this cohort, only four out of five women received surgery and only two out of three received chemotherapy, clearly indicating a need for access to therapy. Higher stage, residual tumor and lack of chemotherapy impaired the outcome of epithelial ovarian cancer cases. This shows the need for gynecologic oncology surgeons training in Ethiopia to provide access to adequate surgery and chemotherapy. Although almost half of the patients presented with FIGO stage III or IV tumors, only 29% received pain medication underlining the need to expand access to pain management and palliative care.

Acknowledgments

This work was supported by the Federal Government German Ministry of Education for Development and Research (grant number 01DG12006), by the American Cancer Society, and by the World Health Organization country office.

Author Contributions

Conception/design: Swantje Piszczan, Dawit Desalegn, Hezkiel Petros, Mengistu Gurmu, Eric Sven Kroeber, Adamu Addissie, Rafael Mikolajczyk, Rahel G. Ghebre, Assefa Mathewos, Christoph Thomssen, Ahmedin Jemal, Eva Johanna Kantelhardt

Provision of study material or patients: Dawit Desalegn, Hezkiel Petros, Mengistu Gurmu, Assefa Mathewos

Collection and/or assembly of data: Swantje Piszczan, Dawit Desalegn, Hezkiel Petros, Mengistu Gurmu, Eric Sven Kroeber

Data analysis and interpretation: Swantje Piszczan, Adamu Addissie, Rafael Mikolajczyk, Rahel G. Ghebre, Christoph Thomssen, Ahmedin Jemal, Eva Johanna Kantelhardt

Manuscript writing: Swantje Piszczan, Dawit Desalegn, Hezkiel Petros, Mengistu Gurmu, Eric Sven Kroeber, Adamu Addissie, Rafael Mikolajczyk, Rahel G. Ghebre, Assefa Mathewos, Christoph Thomssen, Ahmedin Jemal, Eva Johanna Kantelhardt

Final approval of manuscript: Swantje Piszczan, Dawit Desalegn, Hezkiel Petros, Mengistu Gurmu, Eric Sven Kroeber, Adamu Addissie, Rafael Mikolajczyk, Rahel G. Ghebre, Assefa Mathewos, Christoph Thomssen, Ahmedin Jemal, Eva Johanna Kantelhardt

Disclosures

Christoph Thomssen: Amgen, Astra-Zeneca, Celgene, Daiichi Sankyo, Eisai, Eli Lilly & Co., Merck Sharp & Dohme, Nanostring, Novartis, Pfizer, Puma, Roche (H, SAB), American Diagnostica,

Affymetrix, Nanostring (RF). 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

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Vulvar cancer in Ethiopia

A cohort study on the characteristics and survival of 86 patients

Eric Sven Kroeber, MD[a], Assefa Mathewos, MD[b], Tigeneh Wondemagegnehu, MD[b], Abreha Aynalem, MD[b], Tufa Gemechu, MD[c], Swantje Piszczan, MD[d], Genebo Timotewos, BS[b], Adamu Addissie, MD, MPH, MA[e], Andreas Wienke, PhD[a], Susanne Unverzagt, PhD[a], Christoph Thomssen, MD[d], Ahmedin Jemal, DVM, PhD[f], Eva Johanna Kantelhardt, MD[a,g,*]

Abstract

Vulvar cancer (VC) is strongly associated with human papilloma virus (HPV) infections and immunosuppression (e.g., HIV). However, there is limited information on VC patient characteristics and survival in parts of sub-Saharan Africa, including Ethiopia, where chronic HPV and HIV infections are prevalent. The aim of this study is to provide a first view on VC patient characteristics in a sub-Saharan African setting.

We present a retrospective analysis of records of 86 VC patients diagnosed between January 2010 and October 2015 at Addis Ababa University Hospital and other major health facilities in Ethiopia. Follow-up for vital status was obtained by telephone contact with patients or relatives. The primary endpoint was all-cause mortality.

The median age of the patients was 39 (range: 20–85) years, 83% with known HIV status were positive and 81% presented with FIGO stages 2 or 3. The median follow-up time for surviving patients was 17 months (range: 0.1–65.0 months). The 1- and 2-year survival rates were 80% and 51%, respectively. Approximately 37% of patients received surgery, 38% received radiotherapy, and 33% received chemotherapy. Patients who received therapy had better survival than those who did not [adjusted hazard ratios: surgery, 0.44 (95% CI, 0.19–1.03); radiotherapy, 0.36 (95% CI, 0.14–0.90); chemotherapy, 0.42 (95% CI, 0.15–1.12)].

A substantial proportion of VC patients in Ethiopia present at a late stage and receive suboptimal treatment. HIV infections appear to be a common comorbid condition. These conditions result in poor outcomes.

Abbreviations: AA = Addis Ababa, AACCR = Addis Ababa City Cancer Registry, ART = antiretroviral therapy, CI = confidence interval, FIGO = International Federation of Gynecology and Obstetrics, HPV = human papilloma virus, HR = hazard ratio, ICD-O-3 = International Classification of Disease-Oncology-3, SEER = Surveillance, Epidemiology, and End Results Program, VC = vulvar cancer.

Keywords: cumulative survival rate, HIV infections, sub-Saharan Africa, Ethiopia, vulvar neoplasms

1. Introduction

Vulvar cancer (VC) is a rather rare cancer entity, but its incidence has been increasing steadily in recent decades worldwide.[1–5] While in 2007 an estimated 3490 women were diagnosed with and 880 died of VC in the United States, this number rose to 5950 diagnoses and 1110 deaths in 2016.[6,7] Population-based data from the East African countries of Uganda, Zimbabwe, and Malawi show age-standardized incidence rates of 0.6, 1.1, and 1.0 per 100,000 women per year, respectively.[8–10] With an estimated population of 105.0 million people (2017), Ethiopia is the second most populated country in sub-Saharan Africa.[11] Data from Addis Ababa City Cancer Registry (AACCR) show an age-standardized incidence of 1.4 cases of VC per 100,000 women per year in Addis Ababa (AA) (2012 and 2013).[12] Squamous cell carcinoma is the most common histologic type (90%).[13] There are 2 different types: one linked to human papilloma virus (HPV) infection, histologically nonkeratinizing and more common in younger women. Risk factors include impaired immunological status (e.g., HIV coinfection) and smoking. The second is HPV-independent, histologically keratinizing, and not related to HPV infection or smoking. VC is more common in older women with chronic dystrophic diseases (e.g., lichen sclerosis).[14,15] HIV-positive women have a higher risk of VC.[16]

Early-stage VC treatment has high cure rates with low morbidity by radical local excisions with surgical evaluation of lymph nodes. In advanced diseases, surgery and chemoradiation are recommended.[17] The 5-year relative survival rate of VC patients diagnosed from 2006 to 2012 in the United States, based

Editor: YX Sun.

Funding: This work was supported by the German Ministry for Economic and Development Cooperation (BMZ) through the ESTHER University and Hospital Partnership Initiative of German International Cooperation (GIZ). This work was also supported by Intramural Funding from the Research Department of the American Cancer Society. We acknowledge the financial support of the Open Access Publication Fund of the Martin-Luther-University, Halle-Wittenberg, Germany. We thank the staff of the radiotherapy center of Addis Ababa University Hospital and the Addis Ababa City Cancer Registry, Ethiopia.

The authors have no conflicts of interest to disclose.

[a] Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University, Halle an der Saale, Germany, [b] Radiotherapy Center, [c] Department of Pathology, Addis-Ababa-University, Addis Ababa, Ethiopia, [d] Department of Gynecology, Martin-Luther-University, Halle an der Saale, Germany, [e] School of Public Health, Addis-Ababa-University, Addis Ababa, Ethiopia, [f] American Cancer Society, Atlanta, GA, [g] Department of Gynecology; Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University, Halle an der Saale, Germany.

[*] Correspondence: Eva Johanna Kantelhardt, Department of Gynecology, Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University, Ernst-Grube Str. 40, 06097 Halle an der Saale, Germany (e-mail: eva.kantelhardt@uk-halle.de).

Medicine (2018) 97:9(e0041)

Received: 11 December 2017 / Received in final form: 4 February 2018 / Accepted: 7 February 2018

http://dx.doi.org/10.1097/MD.0000000000010041

on the Surveillance, Epidemiology, and End Results Program (SEER) 18 database, is 71.9%.[18] Population-based data from England showed a 1-year survival rate of patients diagnosed between 2007 and 2009 of 85.2%.[3] The outcome varies greatly between early- and late-stage diseases. In a study by Homesley et al,[19] patients with a minimal risk had a 5-year survival rate of 98%; of patients with high risk, only 29% survived 5 years. Between 2009 and 2013, the median age at diagnosis in the SEER population was 68 years.[18] In England, Lai et al[3] reported significantly rising incidence rates in younger women aged 20 to 59 years from 1990 to 2009. This development is attributed to growing numbers of HPV-related cancers.[20]

The objective of our study is to provide the first insights into VC-patients demographics, tumor characteristics, treatment, and resulting overall survival in Ethiopia.

2. Methods

2.1. Patients and methods

This hospital cohort study included 86 Ethiopian women who were diagnosed with VC between January 2010 and October 2015. We included patients from the Radiotherapy Center and the Pathology Department of Tikur Anbessa Specialized University Hospital as well as AACCR. Data were collected between October 5 and November 6, 2015. We found 86 patients admitted for VC. Of these, 81 had a histologically verified primary diagnosis of malignant neoplasm of the vulva [International Classification of Disease-Oncology codes C51.0-9]; 3 were cytologically diagnosed and 2 clinical diagnosis only. In 51 cases, all patient, tumor, therapy, and outcome information was abstracted from patients' files. In 35 cases only limited information was available from the AACCR database including date of diagnosis and last contact, basis of diagnosis, tumor topography, and morphology according to ICD-O-3, age, and planned treatment; no information on HIV status was available. We suspected a potential source of bias in difficulties including patients who died early; however, those patients included from the AACCR were included at first timepoint of diagnosis and therefore included irrespective of early death.

Patients or relatives were contacted via telephone to collect information on survival (n = 80) between November 1 and November 13, 2015. For 6 patients without telephone numbers available, the last date of contact was taken from files.

In case of contradicting information between the files and the relatives on dates of death (n = 8), the following rules applied: if the date of death given by relatives was before the last date "patient alive" in the file, we assumed that the patient died 3 months after the date in the file. The 3 months were chosen since patients were appointed 3-monthly for follow-up; a missed appointment and known death was thus approximated.

2.2. Staging

Tumors were classified according to the International Federation of Gynecology and Obstetrics (FIGO) staging system.[21] Tumor size (T), lymph node status (N), and metastasis (M) mentioned in the files within the first 3 months after primary diagnosis were used as baseline characteristics (n = 48). Because of the lack of detail on lymph node status in 32 cases, we decided to group stages 1 to 3 into one category since lymph node status is the defining factor to distinguish between these stages. Patients without known lymph node status were classified stages 1 to 3 because we assumed that a stage 4 (="fixed or ulcerated inguinofemoral lymph nodes") would have been mentioned in the file.

2.3. Treatment modalities

Information on treatment was abstracted from patient medical files (n = 51). If treatment information seemed to be incomplete and for AACCR cases, we used additional information from the follow-up call (n = 37) or AACCR database only (n = 5).

Patients with VC were referred from all over Ethiopia for chemoradiation, because Tikur Anbessa University Hospital has the only cobalt-60 teletherapy unit in Ethiopia. Surgery was performed if the tumor was considered resectable. Individually, a trial of neoadjuvant chemotherapy or chemoradiation was considered to achieve downstaging for better surgical options. Patients with good performance status received 54 to 60 Gy with concurrent chemotherapy (6 cycles of Cisplatinum 60 mg/m^2 + 5-Fluorouracil 475–500 mg/m^2). Patients who were lymph node positive after surgery received 50 to 60 Gy adjuvant radiotherapy. For palliative treatment, patients received 30 Gy.

2.4. Statistical analysis

The primary endpoint of this study was overall survival. Person time equaled the time from the date of pathologic diagnosis to the date of last contact or death. The survival probabilities were estimated using the Kaplan–Meier method. Multivariate Cox proportional hazard regression analysis was used to estimate adjusted hazard ratios (HR) and corresponding 95% confidence intervals (CI) for prognostic factors. The *P* values are considered as explorative. The median follow-up time for surviving patients was 17 months (range, 0.1–65.0). Sensitivity analysis was performed on the subgroup of known HIV-positive patients.

Ethical approval was acquired from the AA Medical Faculty and Martin-Luther-University Halle Review Board. Our study was executed without individual informed consent because the data were retrospectively obtained from routine care documentation.

3. Results

3.1. Patient characteristics and therapy

The majority of the 86 patients in this study came from AA (76%). The median age was 39 years (range, 20–85 years). The mean number of children was 3.3 (range, 0–14). None of the patients mentioned ever having smoked. Forty out of 48 patients had FIGO stages 1 to 3 cancer (83%). It is notable that only 1 case would have been classified as stage 1 with a given negative lymph node status. Squamous cell carcinoma was most common (87%). Tumor grading was available in only 11 cases; of those, 73% were well differentiated. Mean tumor size was 7 cm. Information on HPV was not available.

A total of 33 patients (38%) received radiotherapy. In 16 cases, detailed information on radiotherapy was available: 8 patients received 40 Gy in 20 fractions, 6 patients received 30 Gy (n = 5 in 10 fractions, n = 1 in 15 fractions), 1 patient received 60 Gy (30 fractions), and 1 patient received 20 Gy (10 fractions).

Thirty-two patients (37%) received surgery. Surgical procedures were mentioned in 7 cases; 3 patients received a local excision, 2 were treated by hemi-vulvectomy, and 2 by vulvectomy.

A total of 28 patients (33%) received chemotherapy. Of them, in 16 patients with additional information received Cisplatinum/5-Fluorouracil; of those, 11 completed 6 cycles of treatment. Three patients' files ended after 2 cycles of chemotherapy, 1 patient received only 1 cycle, and in 1 case, no information on the number of cycles was available (Table 1).

Table 1

Clinical and pathological characteristics.

			HIV status (n = 36)			
	Total (n = 86)	%	Positive (n = 29)	%	Negative (n = 6)	%
Place of origin						
Addis Ababa	65	75.6	20	69.0	3	50
Non-Addis Ababa	21	24.4	9	31.0	3	50
Age, y						
<30	10	11.6	1	3.4		
30–39	33	38.4	25	86.2		
40–49	11	12.8	1	3.4	1	16.7
50–59	13	15.1	1	3.4	1	16.7
60–69	10	11.6	1	3.4	3	50.0
≥70	9	10.5			1	16.7
Parity						
0–1	14	31.8	13	50		
2–3	17	38.6	10	38.5	1	16.7
>3	13	29.5	3	11.5	5	84.3
Marital status						
Single	5	19.2	4	21.1		
Married	11	42.3	7	36.8	1	100
Divorced	5	19.2	4	21.1		
Widowed	5	19.2	4	21.1		
Stage (FIGO)						
1–3	40	83.3	22	75.9	6	100
4	8	16.7	5	17.2		
Histology						
Squamous cell carcinoma	75	87.2				
Keratinizing	25	29.1	10	34.5	2	33.3
Nonkeratinizing	12	14.0	5	17.2	1	16.7
NOS	38	44.1	10	34.5	3	50.0
Carcinoma NOS	5	5.8	1	3.4		
Adenocarcinoma	1	1,2				
Verrucous carcinoma NOS	1	1,2				
Unspecified	4	4.7	3	10.3		
Grading						
Well-differentiated	8	9.3	3	75.0		
Moderately differentiated	1	1.2				
Poorly differentiated	1	1.2	1	25.0		
Undifferentiated	1	1.2				
Unknown	75	87.2				
Tumor size (mean, SD)	7.00 ± 4.15 cm		7.64 ± 4.36 cm		8.00 ± 4.69 cm	
Surgery						
Yes	32	37.2	6	20.7	1	16.7
No	54	62.8	23	79.3	5	83.3
Radiotherapy						
Yes	33	38.4	13	44.8	4	66.7
No	53	61.6	16	55.2	2	33.3
Chemotherapy						
Yes	28	32.6	8	27.6	2	33.3
No	58	67.4	21	72.4	4	66.7

FIGO = International Federation of Gynecology and Obstetrics, NOS = not otherwise specified, SD = standard deviation.

3.2. HIV characteristics

Of 51 patients with a file available, information about HIV status was reported for 35 patients (found in 69% of files, n = 16 unknown) and 83% (n = 29) of these were HIV positive. Ninety percent of the HIV-positive patients were younger than 40 years (n = 26); only 3 were above 40 years old (10%). None of the known HIV-negative patients was younger than 40 years. Most patients were on antiretroviral therapy (ART) treatment at the time of diagnosis (86%; n = 25) and the mean time from the start of ART to VC diagnosis was 40.7 months (range, 29.8–84.1 months). Among the 10 patients with known WHO-HIV stage, 90% were stage 4. Patients with known HIV-positive status were more likely to receive radiotherapy (HIV-positive, 45%; HIV-negative, 57%) compared with the total cohort (38%) but less likely to receive surgery (HIV-positive, 21%; HIV-negative, 17%; total cohort, 37%). The proportion of patients receiving chemotherapy was generally similar among the 3 groups of patients (approximately 30%) (Table 2).

3.3. Survival

Of the 51 patients with files available, 29 returned for regular follow-up visits (57%) with a median of 19 months (range, 8–58).

Table 2

Characteristics of HIV-positive patients (n = 29).

	All patients known HIV positive (n = 29)
ART at point of diagnosis? yes/no	25 (86%)/4 (14%)
WHO Stage at point of diagnosis Stage $^{3}/_{4}$	1 (10%)/9 (90%)
CD4 cell count (done ±4 mo from diagnosis) (n = 10)	
Mean cells/mm^3 [SD]	415 [230–600]
Minimum/maximum	200/750
Time from start of ART to diagnosis (mo) (n = 23)	
Mean [range]	40.7 [−29.8–84.1]

ART = antiretroviral therapy, SD = standard deviation.

Twenty-two women (43%) did not have regular follow-up visits (maximum follow-up time: 8 months after primary diagnosis).

Of all women 34 died during follow up. The cumulative overall survival rate after 1 and 2 years was 80% and 51%, respectively, with a median survival of 33 months (95% CI: 10–55) (Fig. 1).

The survival of patients receiving surgery (adjusted HR, 0.44; 95% CI, 0.19–1.03), radiotherapy (HR 0.36; 95% CI 0.14–0.90), or chemotherapy (HR, 0.42; 95% CI, 0.15–1.12) tended to be prolonged compared to those without these therapies (Fig. 2). FIGO stage 4 patients had unfavorable outcomes (adjusted HR = 2.06; 95% CI, 0.75–5.62) compared to patients stage 1 to 3 (Table 3).

4. Discussion

Our study is the first to provide patient characteristics and survival for VC patients in a sub-Saharan African setting. The median age was 39 years; a high rate of patients with information available were HIV positive (n = 29, 83%). Ninety percent of the HIV-positive patients were younger than 40 years (n = 26). The 1- and 2-year survival rates for all VC patients were 80% and 51%, respectively. Surgery and radiotherapy were received by 37% and 38% of the patients, respectively; 33% received chemotherapy.

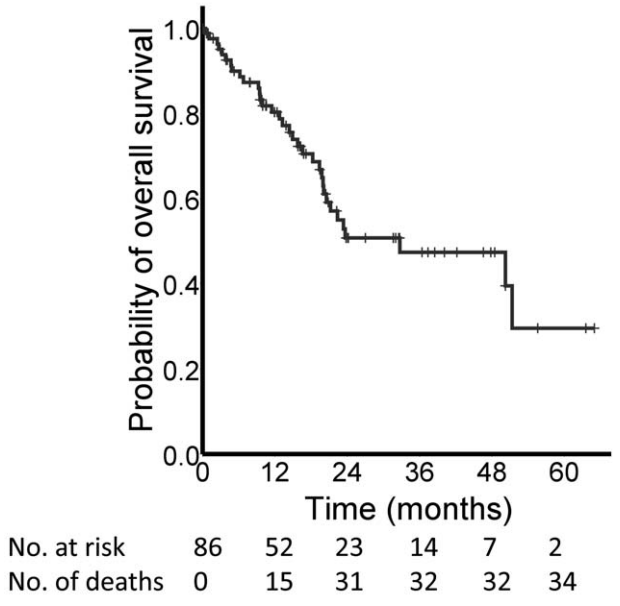

Figure 1. Cumulative overall survival probability of the total cohort of VC patients. No. = number, VC = vulvar cancer.

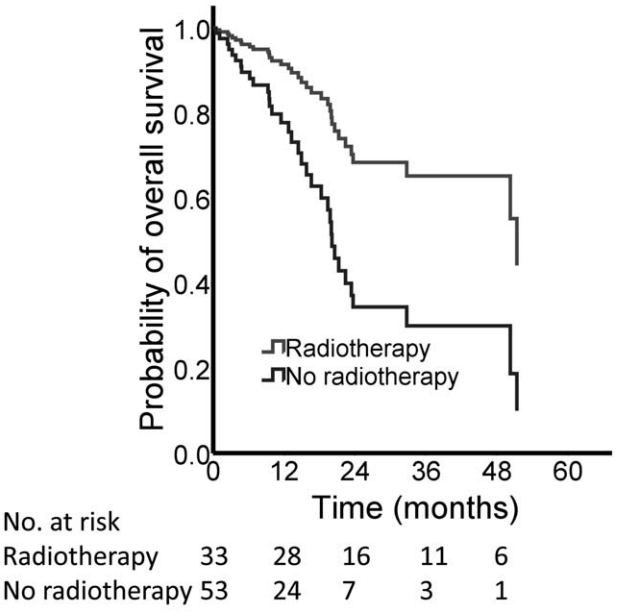

Figure 2. Probability of overall survival for VC patients stratified by radiotherapy received or not received. Adjusted for age (binary), FIGO stage, surgery, and chemotherapy. No. = number, VC = vulvar cancer.

4.1. Age

With a median age of 38 years, the cohort was considerably younger than patients in, for example, the United States (SEER, 68 years).[18] A study from Germany shows a change in the mean age of diagnosis from 65.6 years in the 1980s to 57.0 years around the year 2000. In the first period, 11% of patients diagnosed were under 50 years of age, whereas in the second, this share rose to 41%, probably due to growing numbers of HPV-related cancers.[20] In our hospital-based cohort, the low median age is attributable to the young population structure in Ethiopia.[22] We noted that gynecologists in low-resource settings have to treat young patients with VC and treatment plans (especially surgery) must consider sexually active premenopausal women.

4.2. HIV

The proportion of HIV-positive patients is high, especially in the age group below 40 years. We assumed that most of the patients of unknown HIV status were negative, because VC appears

Table 3

Unadjusted and adjusted HRs for death.

Characteristic	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Age (per additional year)	1.01 (0.98–1.03)	.53	1.01 (0.98–1.03)	.65
FIGO (Stage 1–3*)				
Stage 4	2.05 (0.80–5.24)	.14	2.06 (0.75–5.62)	.16
Unknown	0.70 (0.34–1.63)	.46	0.55 (0.23–1.30)	.17
Surgery (yes vs no*)	0.47 (0.21–1.03)	.06	0.44 (0.19–1.03)	.06
Radiotherapy (yes vs no*)	0.40 (0.19–0.82)	.01	0.36 (0.14–0.90)	.03
Chemotherapy (yes vs no*)	0.31 (0.14–0.70)	.01	0.42 (0.15–1.12)	.08

CI = confidence interval, FIGO stage = International Federation of Gynecology and Obstetrics stage, HR = hazard ratio.

Adjusted for surgery, chemotherapy, age (binary), and FIGO stage (* reference category).

primarily in HIV-positive patients with low CD4 T-cell counts[23]; such HIV-positive patients would have been clinically suspicious and received a test. Altogether, this would result in an estimated proportion of 57% HIV-positive cases among the subgroup in our cohort with files available. This estimate is consistent with data from Cape Town, South Africa; 50% (in 2014) and 41% (in 2015) of VC patients were HIV-positive.[15] It is notable that the HIV prevalence in South Africa was 19.2% in 2015, while the HIV prevalence in Ethiopia was merely 2.3% in 2012 (4.4% in AA).[24,25] Despite the lower prevalence of HIV in Ethiopia, there is a similarly high rate of HIV positivity in our cohort. We propose that every VC patient should be tested for HIV.

We do not think that morbidity due to HIV had a large effect on our VC patients' overall survival time. Most patients had long been on ART at the point of diagnosis for a mean time of more than 3 years. Studies from Ethiopia and Uganda showed that HIV morbidity is very low 2 years after ART initiation.[26,27] Of 10 patients with known WHO-HIV stage, all but one were stage 4. This probably led to lower proportions of HIV-positive patients receiving surgery, radiotherapy, or chemotherapy. Patients with known HIV-positive status should easily be checked for VC in addition to cervical cancer screening in the same procedure by simple inspection.

Because HIV is a risk factor for the HPV-related VC type, information on HPV status would be very interesting.[15] Unfortunately, no patient was tested for HPV. A population-based cohort with complete information would be needed to assess the impact of HIV and HPV on the incidence of VC in Ethiopia.

4.3. Survival

The 1-year survival rate was almost as high as the survival rate of VC patients from England (2003–2005; 83.1%). Whereas the 5-year survival rate of the English cohort was still 69.9% (SEER database 71.9%),[18] the 2-year survival of the Ethiopian cohort already decreased to 51%.[3] This is probably due to advanced stage—only one patient in our cohort met the criteria for FIGO stage 1, whereas 43% of patients in the English study with FIGO stage available were stage 1.[3] More awareness among health care workers and the community could possibly achieve downstaging.

Another contributing factor for lower survival in Ethiopia is the lack of standard treatment. There are long waiting times until the start of radiotherapy because there is only one radiotherapy machine for the country. A study on cervical cancer patients in Ethiopia found that the FIGO stage increased considerably between the point of diagnosis and the start of treatment (waiting time 3.8 months).[28] In our study, waiting times were even longer (median of 7.3 months). This highlights the urgent need to increase radiotherapy capacity in the country.

In cases where patients received radiotherapy, they tended to have longer survival (HR 0.36; 95% CI, 0.14–0.90). Surgery and chemotherapy, also tended to be associated with prolonged survival (HRs 0.44, 95% CI, 0.19–1.03 and 0.42; 95% CI, 0.15–1.12, respectively). These finding are in line with current treatment concepts that include surgery, radiotherapy, and chemotherapy.[17]

4.4. Limitations

There are limitations to our retrospective study: Nodal status was available in only 16 cases, limiting precise information on FIGO stage. Therefore, we decided to group stages 1 to 3, because nodal status is the defining factor for stage 3. For the 35 cases for whom there were no patient files, little information on patient characteristics was available. HIV status was absent in 51 cases. We assume that, even without complete information on all patients, our findings contain valuable insight into VC patients in a sub-Saharan setting. Second, we were unable to include cases from the surgical departments of TAH. This presumably led to a reduced number of patients with early-stage cancers who were treated by surgery only. According to the information provided by gynecologists, we assume that those were few cases. Third, because recently VCs are grouped into HPV-associated and non-HPV associated cancers, information on HPV would have been of high interest. To date, there is no option for HPV testing in Ethiopia. Fourth, the date of death obtained from family members during the follow-up call was sometimes vague, leading to a lack of precision in survival time. We assume that the error was in both directions and thus did not affect the results.

Despite these limitations, our study adds new information on a previously underexplored type of cancer to the literature, because it is the first to describe the characteristics and outcome of more than 50 VC patients in a sub-Saharan African setting.

5. Conclusion

This is the first study to describe the characteristics and outcome of VC patients on the basis of 86 patients diagnosed between 2010 and 2015 in AA. Even patients with late stage presentation, due to the nature of slow-growing tumors, usually survive the first year. Our 2-year survival rapidly declined due to the limited treatment options and urgently highlights the need for palliative care. The very low median age of 39 years probably results from the young population structure in Ethiopia. The surprisingly high share of 57% HIV-positive patients does not reflect the HIV prevalence in Ethiopia of 3.2%. Due to the high HIV positivity rate, we suggest that all VC patients should be tested and HIV patients should have an inspection of the vulva during cervical cancer screening. FIGO stage 4 was related to worse outcome. Treatment had a positive effect on patient survival, despite long waiting times until the start of radiotherapy and resulting urgent need for more than one radiotherapy facility in Ethiopia. Ginsburg et al[29] recently described the vast discrepancies between breast and cervical cancer patients in low- and high-come countries. Similar disparities can be seen in VC, highlighting the crucial necessity of an increasing awareness of women's cancers and their priority in women's health policies, including preventive measures, treatment options, and patient education to reduce the high frequency of patients with FIGO stage 4 who do not receive treatment and the resulting poor prognosis.

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Selbstständigkeitserklärung

Ich erkläre hiermit, die Arbeit selbstständig geschrieben und keine anderen als die angegebenen Quellen genutzt zu haben.

Halle (Saale), den 03.01.2021 Swantje Piszczan

Erklärung über frühere Dissertationsversuche

Diese Arbeit habe ich im Rahmen meines ersten Dissertationsversuches geschrieben. Ich habe diese Arbeit ausschließlich an der Medizinischen Fakultät der Martin-Luther-Universität Halle- Wittenberg als Dissertationsschrift eingereicht.

Halle (Saale), den 03.01.2021 Swantje Piszczan