Medizinische Fakultät der Martin-Luther-Universität Halle-Wittenberg

Auswertung von Daten des populationsbezogenen Krebsregisters und Überleben von Patientinnen mit Vulvakarzinom in Addis Ababa

Dissertation

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Referat

In dieser Arbeit werden zusammenfassend die Ergebnisse einer deskriptiven Untersuchung und einer explorativen Studie dargestellt. In ersterer werden Inzidenzen und Verteilung von Krebserkrankungen in den Jahren 2012 und 2013 in Addis Ababa, Äthiopien, beschrieben, die vom populationsbezogenen Krebsregister in Addis Ababa erfasst wurden. Letztere fasst die Ergebnisse einer retrospektiven Kohortenstudie zusammen: Charakteristika und Prognose von Vulvakarzinompatientinnen, die in den Krankenhäusern von Addis Ababa diagnostiziert und behandelt wurden. Ziel dieser Arbeit ist die Verbindung einer epidemiologischen, populationsbezogenen Analyse der Verteilung von Krebserkrankungen als allgemeinerem Aspekt der Krebsforschung mit der Beschreibung der Charakteristika und des Überlebens einer bisher selten beschriebenen Karzinomentität (Vulvakarzinom) als speziellerem Aspekt.

Die altersstandardisierte kumulative Inzidenz (ASR) von Krebserkrankungen in Addis Ababa beträgt 136/100.000 für Frauen und 70/100.000 für Männer im Zeitraum 2012-2013. Etwas mehr als zwei Drittel (68 %) der Karzinomfälle in Addis Ababa treten bei Frauen auf. Bei diesen sind die drei häufigsten Entitäten das Mammakarzinom (31,5 %; ASR: 40,6), das Zervixkarzinom (14,1 %; ASR: 21,5) und das Ovarialkarzinom (6,3 %; ASR: 8,5). Krebsfälle bei Männern machen 32 % der Krebsfälle in Addis Ababa aus. Die häufigsten Entitäten sind das kolorektale Karzinom (10,6 %, ASR: 7,6), das Non-Hodgkin-Lymphom (10,2 %, ASR: 6,8) und das Prostatakarzinom (6,9 %, ASR: 6,4). Die altersstandardisierte Inzidenz für das Vulvakarzinom liegt bei 1,5/100.000. Das mediane Alter bei Erstdiagnose liegt in Äthiopien bei 39 Jahren. Die Überlebensrate liegt nach einem Jahr bei 80 % und sinkt nach zwei Jahren auf 51 %. Patientinnen, die eine der drei Therapieoptionen Radiotherapie (HR= 0,36; 95% KI= (0,14;0,90)), operative Versorgung (HR= 0,44; 95% KI=(0,19;1,03)) und Chemotherapie (HR= 0,42; 95% KI=(0,15;1,12)) erhalten hatten, hatten tendenziell eine verlängerte Überlebenszeit. Etwa 57 % der Patientinnen waren HIV-positiv.

Diese Ergebnisse werden mit Daten aus anderen Ländern Subsahara-Afrikas sowie Westeuropas und den USA verglichen. Die gewonnenen Erkenntnisse sollen in Handlungsempfehlungen zur besseren Gesundheitsversorgung in der Region umgesetzt werden.

Kröber, Eric Sven: Datenauswertung eines populationsbezogenen Krebsregisters und das Überleben von Vulvakarzinompatientinnen in Addis Ababa. Halle, Univ., Med. Fak., Diss., 10 Seiten, 2018

Report

This dissertation summarizes the results of two explorative studies. In the first one describes the incidence and distribution of cancer entities in 2012 and 2013 in Addis Ababa, Ethiopia. The population-based Addis Ababa City Cancer Registry provided the data for this study. The second study is a retrospective cohort study on the characteristics and outcome of vulvar cancer patients who were treated in major health facilities in Addis Ababa between 2010 and 2015. The objective of this dissertation is to combine an epidemiologic, population-based analysis of the distribution of cancer entities as a more general aspect of cancer research with the description of the characteristics and outcome of patients suffering from a rather rare cancer entity (vulvar cancer) as a more specific facet.

The age-standardized incidence rates of cancers in Addis Ababa were 136/100,000 for females and 70/100,000 for males in 2012 and 2013. About two thirds (68 %) of all cancers occurred in females. For them the most common sites were cancers of the breast (31.5 %; ASR: 40.6), cervix uteri (14.1 %; ASR: 21.5) and ovary (6.3 %; ASR: 8.5) while colorectal cancer (10.6 %, ASR:7.6), non-Hodgkin lymphoma (10.2 %, ASR: 6.8) and prostate cancer (6.9 %, ASR: 6.4) were the most frequent in males.

The age-standardized incidence rate of vulvar cancer was 1.5/100,000. The median age at the point of diagnosis was 39 years. The cumulative overall survival rate after one year was 81 % and rapidly declined to 51 % after two years. The survival time of 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 be prolonged. About 57 % of patients were HIV-positive.

These results are compared with data from other sub-Saharan African countries as well as Western European countries and USA. Furthermore, the findings are used to provide practical advice in order to improve the quality of health care in the region.

Kröber, Eric Sven: Datenauswertung eines populationsbezogenen Krebsregisters und das Überleben von Vulvakarzinompatientinnen in Addis Ababa. Halle, Univ., Med. Fak., Diss., 10 Seiten, 2018

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Verzeichnis der Abkürzungen und Symbole

ASR – Altersstandardisierte kumulative Inzidenz bezogen auf eine Bevölkerung von 100.000 Menschen

FIGO - International Federation of Gynecology and Obstetrics

HIV – Humanes Immundefizienz-Virus

HPV – Humanes Papillom-Virus

HR – Hazard Ratio

ICD – International Classification of Disease-Oncology-3

KI - Konfidenzintervall

1 Einleitung und Zielstellung

Karzinomerkrankungen verursachen weltweit einen großen Teil der Morbidität und Mortalität. Folgen sind unter anderem persönliches Leid, Zerbrechen von Familienstrukturen, Stigmatisierung sowie sozioökonomische Schwierigkeiten (Ferlay et al., 2010). Weltweit gibt es drastische Unterschiede bezüglich Aufklärung und Bildung über Krebsleiden, Möglichkeiten der Diagnostik und Verfügbarkeit der Therapieoptionen. In Ländern mit niedrigem und mittlerem Einkommen gibt es deutlich schlechtere Strukturen zur Versorgung von Karzinompatienten als in Ländern mit hohem Einkommen (Ginsburg et al., 2017).

Die populationsbezogene Krebsregistrierung wird genutzt, um die Inzidenz, Prävalenz und Verteilung der verschiedenen Entitäten in der Bevölkerung zu messen und aufgrund dieser Ergebnisse die medizinische Versorgung zu planen (Bray et al., 2015). Das Krebsregister von Addis Ababa wurde im September 2011 etabliert. Es ist das erste und bislang einzige populationsbezogene Krebsregister in Äthiopien, dem mit geschätzten 105 Millionen Einwohnern zweitbevölkerungsreichsten Land Afrikas (United Nations, 2017). Im Einzugsgebiet des Krebsregisters von Addis Ababa leben etwas mehr als 3 Millionen Menschen. Im Artikel „First data from a population based cancer registry in Ethiopia“ in der Anlage A dieser Dissertation (Timotewos et al., 2018) wurden die Ergebnisse zu den Inzidenzen aus den Jahren 2012 und 2013 publiziert. In Ergänzung zur epidemiologischen, populationsbezogenen Erfassung von Krebserkrankungen als allgemeinerem Teil von Krebsforschung können in Krankenhauskohortenstudien detailliertere Informationen über die Charakteristika, Diagnostik, Therapie und das Überleben von Patienten spezifischer Krebsentitäten gewonnen werden. In der Studie „Vulvar cancer in Ethiopia – A cohort study on the characteristics and survival of 86 patients” in der Anlage B dieser Dissertation (Kroeber et al., 2018) wurden diese Informationen für Patientinnen mit Vulvakarzinom, die in Addis Ababa zwischen Januar 2010 und Oktober 2015 diagnostiziert wurden, untersucht.

Das Vulvakarzinom ist eine verhältnismäßig seltene Krebsentität. Weltweit wurden über die letzten Jahrzehnte jedoch steigende Inzidenzraten beobachtet (Akhtar-Danesh et al., 2014; Schuurman et al., 2013; Lai et al., 2014; Holleczek et al., 2018). Das Plattenepithelkarzinom ist mit 90 % der häufigste histologische Typ (Hacker et al., 2015). Es gibt zwei histologische Subtypen. Zum einen ein HPV-Infektion-assoziierter, nicht-keratinisierender Typ, der häufiger bei jungen Frauen auftritt und dessen Risikofaktoren einen reduzierten Immunstatus (z.B. im Rahmen einer Infektion mit dem Humanen Immundefizienz-Virus (HIV)) beinhalten. Der zweite Typ ist keratinisierend, tritt häufiger bei älteren Frauen auf und ist mit chronisch-dystrophen

Erkrankungen wie Lichen sclerosus assoziiert (Ueda et al., 2011; Hinten et al., 2018). In Subsahara-Afrika gibt es bisher nur sehr eingeschränkt Informationen zu den Charakteristika und dem Überleben von Vulvakarzinompatientinnen. Diese werden jedoch zunehmend notwendig, da Infektionen mit dem Humanen Papillom-Virus (HPV) und HIV, die in Ländern mit niedrigem und mittlerem Einkommen weit verbreitet sind, zu wichtigen Risikofaktoren des nicht-keratinisierenden Vulvakarzinoms gehören (Saidu, 2016; Sitas et al., 2000).

Ziel dieser Arbeit ist eine epidemiologische Beschreibung der auf Krebserkrankungen zurückzuführenden Krankheitslast in Äthiopien. Dazu erfolgte zum einen eine populationsbezogene Analyse der Verteilung von Krebserkrankungen in Addis Ababa und zum anderen eine detaillierte Beschreibung der Charakteristika und des Überlebens einer bisher selten beschriebenen Krebsentität (Vulvakarzinom). Daraus ergeben sich folgende Fragestellungen:

1 Wie groß ist die altersstandardisierte kumulative Inzidenz von Krebserkrankungen in Addis Ababa bei Männern und Frauen?
2 Wie hoch sind die altersstandardisierten kumulativen Inzidenzen der verschiedenen Krebsentitäten bei Männern und Frauen und welche Entitäten treten am häufigsten auf?
3 Wie hoch ist die altersstandardisierte kumulative Inzidenz des Vulvakarzinoms in Addis Ababa?
4 Welche klinischen und demographischen Charakteristika weisen Vulvakarzinompatientinnen in dieser klinischen Kohorte auf?
5 Wie hoch sind die 1- und 2-Jahres-Überlebensraten von Vulvakarzinompatientinnen und wie verhalten sich diese Ergebnisse im Vergleich mit Daten aus Westeuropa / USA?
6 Welcher Anteil der Patientinnen erhält die verschiedenen Therapieoptionen Radiotherapie, Operation und Chemotherapie und welchen Effekt haben die verschiedenen Therapieoptionen auf das Überleben von Vulvakarzinompatientinnen?

Diese Ergebnisse sollen mit Daten aus anderen Ländern Subsahara-Afrikas sowie Westeuropas und der USA verglichen werden. Damit soll die Evidenz für Handlungsempfehlungen zur besseren Gesundheitsversorgung in der Region geschaffen werden. Diese Dissertation basiert auf den zwei in der Anlage beigefügten Veröffentlichungen und der seit 2009 bestehenden Zusammenarbeit zwischen der Martin-Luther-Universität Halle-Wittenberg und der Universität Addis Ababa.

2 Diskussion

2.1 Krebsverteilung und Inzidenz in Addis Ababa

Die altersstandardisierte kumulative Inzidenz für alle Karzinomerkrankungen lag bei Frauen bei 136,2 Fällen pro 100.000 pro Jahr und war bei Männern mit 70,7 Fällen pro 100.000 pro Jahr etwas mehr als halb so groß. Diese Raten sind vergleichbar mit Reporten aus benachbarten Ländern wie Kenia (Frauen, ASR: 196; Männer, ASR: 167) und dem Sudan (Frauen, ASR: 91; Männer, ASR: 92) Auch die Tendenz der Prädominanz der Frauen mit 68 % der registrierten Fälle ist bereits aus anderen Krebsregistern in Subsahara-Afrika, zum Beispiel in Uganda (57 %), bekannt (Ferlay et al., 2013; Wabinga et al., 2013).

Überraschend war die Spitzenposition des Kolorektalkarzinoms bei männlichen Patienten, die erstmalig in einem solchen Setting beschrieben wird. Das Kolorektalkarzinom ist mit Risikofaktoren des sogenannten westlichen Lebensstils assoziiert. Diese beinhalten Alkoholkonsum, Rauchen, Fettleibigkeit und einen hohen Fleischkonsum (Durko et al., 2014). Bei der Bevölkerung von Addis Ababa handelt es sich um Menschen, die in einer urbanen Region leben und wo ein wachsender Anteil der Bevölkerung einen entsprechenden Lebensstil aufweist, was als Ursache für dieses Ergebnis in der Literatur diskutiert wird (Arnold et al., 2017).

Mammakarzinom und Zervixkarzinom als führende Entitäten bei den Frauen entsprechen den Ergebnissen anderer Krebsregister aus Subsahara-Afrika (Ferlay et al., 2013). Steigende Mammakarzinom-Inzidenzraten über die letzten 20 Jahre sind aus Uganda (3,6 %/Jahr) und Zimbabwe (4,9 %/Jahr) bekannt (Wabinga et al., 2013; Chokunonga et al., 2013). Da eine niedrige Kinderzahl ein Risikofaktor für Brustkrebs darstellt, ist anzumerken, dass die Fertilitätsrate von Frauen aus Addis Ababa bei 1,5 pro Frau liegt, während diese mit 5,5 bei Frauen aus ländlichen Gebieten deutlich höher ist (Central Statistics Agency Ethiopia, 2012). Die hohe Inzidenz gynäkologischer Entitäten unterstreicht die Notwendigkeit der Priorisierung gynäkologischer Krebsprävention, -früherkennung und -therapie sowie der verbesserten Information und Bildung der Allgemeinbevölkerung und der im Gesundheitssystem Beschäftigten in Äthiopien. Weiterhin weisen diese Ergebnisse auf die zunehmend urbanisierte und mit westlichem Lebensstil einhergehende Lebensrealität der Bevölkerung Addis Ababas hin. Eine vertiefende Diskussion des Themas findet sich in der Veröffentlichung „First data from a population based cancer registry in Ethiopia" (Timotewos et al., 2018) in der Anlage B in dieser Dissertation.

Im Rahmen dieser Veröffentlichung habe ich während eines viermonatigen Aufenthaltes in Addis Ababa im Jahr 2015 bei der Datenerhebung mitgewirkt, diese qualitätsgesichert und dazu zahlreiche Rücksprachen mit beteiligten Ärzten, Krankenschwestern und Mitarbeitern des Krebsregisters bezüglich der Arbeitsvorgänge vor Ort gehalten. Weiterhin habe ich die Datenanalyse qualitätsgesichert, Grafiken für die Veröffentlichung erstellt, sowie kritische Rückfragen und Kommentare bei der Überarbeitung der Publikation gegeben.

2.2 Überleben von Vulvakarzinompatientinnen in Addis Ababa

Die altersstandardisierte kumulative Inzidenz des Vulvakarzinoms von 1,5 pro 100.000 Frauen pro Jahr in Äthiopien ist mit den vorliegenden Daten aus Uganda (ASR: 0,6), Zimbabwe (ASR: 1,1) und Malawi (ASR: 1,0) vergleichbar (Wabinga et. al, 2013; Chokunonga et. al, 2013; Dzamalala et. al, 2013). Das junge mediane Alter der Vulvakarzinompatientinnen von 39 Jahren zum Zeitpunkt der Diagnose lässt sich auf die junge Bevölkerungsstruktur in Äthiopien zurückführen. Außerdem ist es möglich, dass es einen hohen Anteil HPV-assoziierter Karzinome gab. Dieser Zusammenhang konnte jedoch aufgrund der mangelnden Möglichkeit der HPV-Testung in Äthiopien nicht überprüft werden. Ein überraschendes Ergebnis war der hohe Anteil von HIV-positiven Patientinnen (57 %). In Kapstadt (Südafrika) berichtet eine Studie ähnliche Ergebnisse von 50 % (2014) und 41 % (2015) HIV-positiver Patientinnen (Saidu, 2016). Daher sollten alle Patientinnen mit Vulvakarzinom auf HIV-Infektion getestet werden. HIV-positive Frauen sollten zudem standardmäßig durch Inspektion während des bereits implementierten Gebärmutterhalskrebsscreenings auf ein mögliches Vulvakarzinom untersucht werden. Dies stimmt mit der grundsätzlichen Empfehlung des Ausbaus von Krebsscreening für HIV-positive Menschen überein (Hessol et al., 2018).
Die 1-Jahres-Überlebensrate der Patientinnen mit Vulvakarzinom lag mit 80 % fast so hoch wie in Europa und den USA. Jedoch liegt die 5-Jahres-Überlebensrate in Studien aus England und den USA bei ca. 70 % (Lai et al., 2013; Howlader et al., 2013), während in der untersuchten Kohorte die 2-Jahres-Überlebensrate rapide auf 51 % sank. Als mögliche Ursachen hierfür werden das vergleichsweise hohe Tumor-Stadium nach Klassifikation der International Federation of Gynecology and Obstetrics (FIGO) zum Diagnosezeitpunkt und lange Wartezeiten bis zum Therapiestart (Median von 7,3 Monaten für Radiotherapie) diskutiert.

Patientinnen, die eine der drei Therapieoptionen (Radiotherapie, Operation, Chemotherapie) erhalten haben, hatten tendenziell längere Überlebenszeiten (Radiotherapie: 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). Dies bestätigt die Wirksamkeit der aktuellen Therapieempfehlungen (Board, P. A. T. E., 2018). Zu beachten ist, dass verschiedene nicht erfasste Faktoren, wie der sozioökonomische oder der Gesundheitsstatus Einfluss darauf nahmen, ob die Patientinnen Therapie erhielten. Insgesamt ist festzuhalten, dass die Verfügbarkeit, insbesondere von Radiotherapie, verbessert werden sollte. In Äthiopien steht bis heute ausschließlich eine Radiotherapieeinheit zur Verfügung.

Für eine vertiefende Diskussion der Ergebnisse verweise ich auf den Artikel „Vulvar cancer in Ethiopia: A cohort study on the characteristics and survival of 86 patients" (Kroeber et al., 2018) im Anhang A der Dissertation.

Meine Aufgabenfelder im Rahmen dieser Studie waren die Konzeption, Diskussion und Rücksprache bezüglich Studiendesign und -durchführung mit verantwortlichen Ärzten des Universitätsklinikums in Addis Ababa (Black Lion Hospital) und den Mitarbeitern des Krebsregisters, sowie die logistische Organisation und Datenerhebung vor Ort. Dies geschah zum Großteil während meines viermonatigen Aufenthalts in Addis Ababa. Im nächsten Schritt habe ich die Daten qualitätsgesichert, ausgewertet, Tabellen und Grafiken erstellt und die Ergebnisse im kollegialen Kreis diskutiert. Die Diskussion erforderte die Recherche von Studien zum Überleben und Charakteristika von Vulvakarzinompatientinnen mit einem Fokus auf Veröffentlichungen aus Subsahara-Afrika. Anschließend habe ich die Veröffentlichung entworfen und mich kritisch mit den Kommentaren und Anmerkungen der Ko-Autoren auseinandergesetzt. Nach der Fertigstellung war ich für die Einreichung der Studie bei internationalen Fachzeitschriften mit den erforderlichen Aufgaben der Formatierung und Beantwortung von Rückfragen der Gutachter verantwortlich.

2.3 Limitationen

Eine erste Begrenzung in den Ergebnissen zu den Inzidenzen der Krebsentitäten des Addis Ababa City Cancer Registry, die aus den meisten afrikanischen Krebsregistern bekannt ist, ist eine mögliche Unterregistrierung, da nicht alle Krebspatienten behandelnden Einrichtungen aufgetretene Fälle an das Addis Ababa City Cancer Registry meldeten (Bullard et al., 2000). Es handelt sich um eine Institution, die auch nur wenige onkologische Patientinnen behandelte. Als zweite Limitation ist die Möglichkeit anzuführen, dass ein relevanter Anteil an Karzinomen erkrankter Menschen zu keinem Zeitpunkt vom offiziellen Gesundheitssystem erfasst wurde. In der urbanen Region Addis Ababa nehmen wir an, dass dieser Effekt vernachlässigbar klein ist

und die Ergebnisse nicht beeinträchtigt. Weiterhin ist die Verfügbarkeit von Neurochirurgie, Lungenchirurgie sowie Abdominalchirurgie in Addis Ababa deutlich limitiert. Dadurch sind Krebsarten, deren sichere Diagnose eine operative Probengewinnung benötigt, vermutlich unterrepräsentiert. Ähnlich führt der Mangel an Immunhistochemie, welcher die Differentialdiagnostik im Bereich der hämatologischen Malignome limitiert, zu einer wahrscheinlich verminderten Anzahl dokumentierter Fälle in diesem Bereich. Eine vierte Limitation stellt die nicht vermeidbare Registrierung von bereits in den Vorjahren diagnostizierten Fällen in den ersten Jahren des Krebsregisters dar (Parkin et al., 2014). In den folgenden Jahren können solche Fälle durch Prüfung von Namensgleichheit innerhalb der Datenbank erkannt werden.

In der Vulvakarzinomstudie war eine erste Limitation das Fehlen von wichtigen Informationen in den Patientenakten und das Fehlen von Akten für 35 der 86 Patientinnen. Informationen zum HIV-Status lagen für 51 Patientinnen vor. Der Lymphknotenstatus war bei nur 16 Patientinnen bekannt, was die Möglichkeit der Einordnung in FIGO-Tumorstadien einschränkte. Aus diesem Grund haben wir uns entschieden, die Stadien 1-3 zusammenzufassen, da der Lymphknotenstatus ein entscheidendes Merkmal zur Differenzierung zwischen diesen ist. Zweitens war es nicht möglich, Fälle der chirurgischen Abteilung des Black Lion Hospitals einzuschließen, wodurch die Anzahl der nur chirurgisch versorgten Patientinnen mit frühen Tumorstadien möglicherweise unterschätzt wurde. Drittens war es nicht möglich, Informationen über den HPV-Status der Patientinnen zu erhalten, da HPV-Testung in Äthiopien zum damaligen Zeitpunkt nicht verfügbar war. Eine vierte Limitation waren die vagen Angaben einiger Familienmitglieder zum Sterbedatum der verstorbenen Patientinnen während des Anrufs in der Nachbeobachtungsperiode. Wir vermuten eine Verzerrung in beide zeitlichen Richtungen und damit einen vernachlässigbaren Effekt auf die Ergebnisse bezüglich der Überlebenszeit.

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Thesen

1. Die altersstandardisierte kumulative Inzidenz von Karzinomerkrankungen in Addis Ababa 2012 – 2013 lag bei Frauen bei 136/100.000 und bei Männern bei 70/100.000.
2. Die drei häufigsten Entitäten in Addis Ababa bei Frauen sind das Mammakarzinom (31,5 % aller Krebserkrankungen; ASR 40,6), das Zervixkarzinom (14,1 % aller Krebserkrankungen; ASR: 21,5) und das Ovarialkarzinom (6,3 %, ASR: 8,5). Die häufigsten Entitäten bei Männern sind das Kolorektalkarzinom (10,6 %, ASR: 7,6), das Non-Hodgkin-Lymphom (10,2 %, ASR: 6,8) und das Prostatakarzinom (6,9 %, ASR: 6,4).
3. Die altersstandardisierte kumulative Inzidenz des Vulvakarzinoms liegt in Addis Ababa bei 1,5/100.000 Frauen.
4. Das mediane Alter bei Erstdiagnose von Vulvakarzinompatientinnen liegt bei 39 Jahren in Äthiopien. Die mittlere Tumorgröße zum Diagnosezeitpunkt beträgt 7 cm (Standardabweichung 4,15 cm). 83 % der Patientinnen werden im FIGO-Stadium 1-3 diagnostiziert, wobei das Stadium 1 sehr unwahrscheinlich ist. Etwa 57 % der Patientinnen sind HIV-positiv.
5. Die geschätzte 1-Jahres-Überlebensrate liegt bei 80 %. Zwei Jahre nach Diagnose sinkt diese auf 51 %.
6. Alle drei Therapieoptionen, Radiotherapie (HR= 0,36; 95% KI= (0,14;-0,90)), Operation (HR 0,44; 95% KI, 0,19-1,03) und Chemotherapie (HR 0,42; 95% KI, 0,15-1,12), haben tendenziell einen positiven Effekt auf das Überleben von Vulvakarzinompatientinnen. Nur bei Radiotherapie war das Ergebnis signifikant (p=0.03).

Anlagen

Anlage A

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

Anlage B

Timotewos G, Solomon A, Mathewos A, Addissie A, Bogale S, Wondemagegnehu T, Aynalem A, Dagnechew H, Bireda W, Kroeber ES, Mikolajczyk R, Bray F, Jemal A, Kantelhardt EJ (2018) First data from a population based cancer registry in Ethiopia. Cancer epidemiology 53: 93-98.

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Vulvar cancer in Ethiopia

A cohort study on the characteristics and survival of 86 patients

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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

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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.

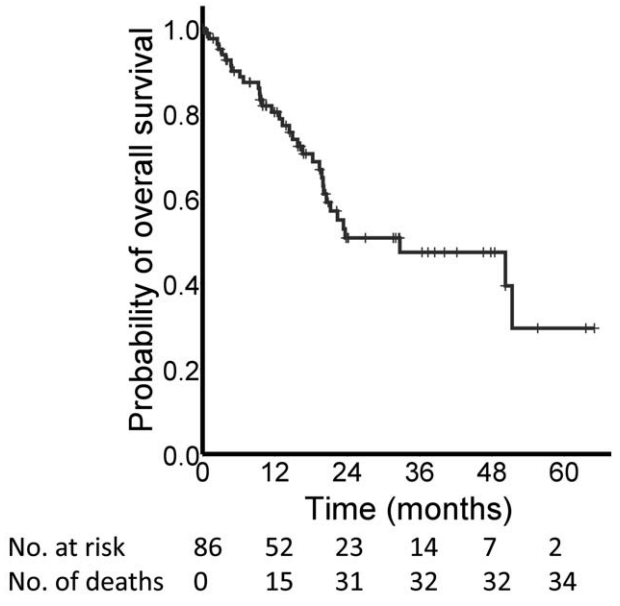

Figure 1. Cumulative overall survival probability of the total cohort of VC patients. No. = number, VC = vulvar cancer.

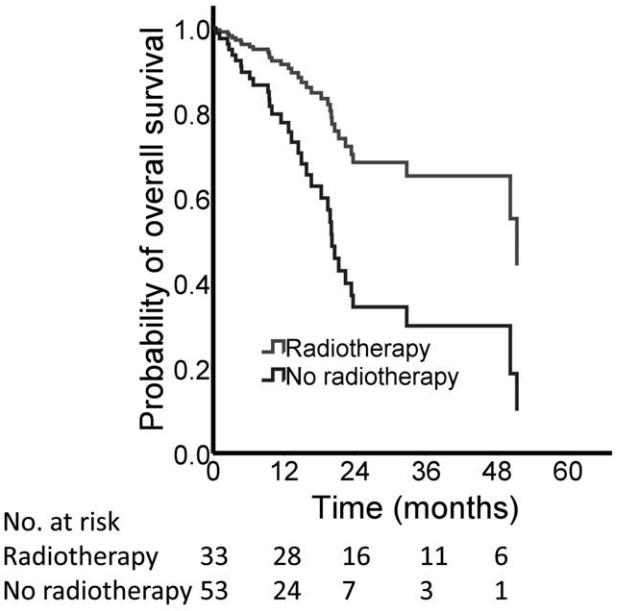

Figure 2. Probability of overall survival for VC patients stratified by radiotherapy received or not received. Adjusted for age (binary), FIGO stage, surgery, and chemotherapy. No. = number, VC = vulvar cancer.

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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First data from a population based cancer registry in Ethiopia

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ABSTRACT

Background: The Addis Ababa City Cancer Registry, established in September 2011, is the only population-based cancer registry in Ethiopia, covering a catchment population of just over three million habitants. Herein, we report incidence data based on the first two years of registration, 2012–2013.

Methods: Newly-diagnosed cancer cases in the capital city were actively collected from 22 hospitals, clinics, and diagnostic facilities.

Results: During 2012–2013, a total of 4139 newly diagnosed cases were recorded, with the majority (67%) occurring in females. Cancers of the breast (31.5%) and cervix (14.1%) were the two most common cancers among females, while colorectal cancers (10.6%) and non-Hodgkin lymphomas (10.2%) were the most common cancers among males. The average annual age-standardized rate for all sites 2012–13 were 136.2 (per 100,000) and 70.7 in females and males, respectively. Female age-standardized rates were 40.6 for breast cancer and 21.5 for cervix, while equivalent rates in males were 7.6 per 100,000 for colorectal cancer and 6.8 per 100,000 for non-Hodgkin lymphoma.

Conclusion: In general, these incidence patterns were similar to those reported in neighboring countries, which suggests that the majority of cancer cases occurring in Addis Ababa are captured within this starting phase of the registry. However, our finding of colorectal cancer as the most commonly-diagnosed cancer in males is novel and requires further investigation.

1. Introduction

1.1. The burden of cancer

Cancer is one of the most important causes of morbidity and mortality, suffering, social and economic problems in the transitioning, as well as in the developed world [1]. There are substantial disparities in diagnosis, care and outcome of cancer in different regions of the world, with females especially impacted by the burden of the disease [2]. This has led to UN-led high-level commitments to tackle cancer among other major non-communicable diseases [3] and now, several African governments have developed and implemented operational national cancer control plans [4,5]. Population-based cancer registries are well-established institutions required to monitor and evaluate specific interventions to reduce the cancer burden; the first cancer registries were established over 70 years ago, and today there are more than 700 cancer

Abbreviations: ICD-O, International Classification of Disease for Oncology; NHL, Non-Hodgkin's lymphoma

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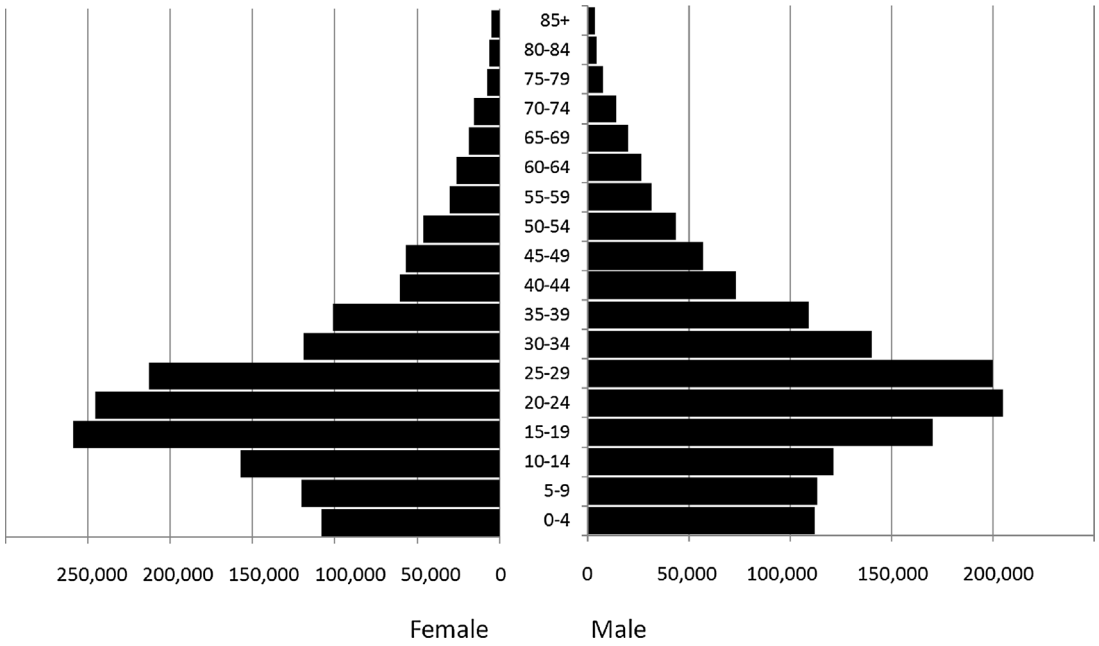

Fig. 1. Addis Ababa City population pyramid estimated for 2012.

registries worldwide [6].

1.2. Population-based cancer registration

In 2014, there were 26 population-based cancer registries from Africa including Addis Ababa that contributed data to the African Cancer Registry Network and to the International Agency for Research in Cancer for specific studies [7,8]. The patterns of cancer incidence vary between the countries in the region, partly reflecting differences in underlying cancer risk. Studies from North Africa, as an example, have suggested that the decline of cancer incidence is due to changes in environmental and lifestyle factors [9], with the key determinants including smoking, alcohol consumption, changes in reproductive patterns, and increasingly westernized lifestyles including more physical inactivity and the eating of foods low in fibre and high in fat [10–12]. Few studies have examined the influence of socioeconomic transitions in Africa on risk factors and cancer burden as well as effects of cancer control programs using population-based incidence data [13,14].

1.3. Addis Ababa cancer registry

The Addis Ababa City Cancer Registry has been collecting incidence data since September 2011. Addis Ababa is by far the largest city in Ethiopia, a country where the majority of the population live in rural areas and are dependent on farming. There are various ethnic groups; the majority are Oromo (34.0%), Amhara (29.8%), Tigray (7.7%) and others. The Amhara group is the most common in Addis Ababa [15]. In Addis Ababa, there is high economic growth, accounting for a Gross Domestic Product of 61.54 billion USD in 2015, with continuous modernization, construction, industrialization and change towards a westernized environment and lifestyle. A number of initiatives by governmental and non-governmental organizations are underway to improve cancer control through implementing the national cancer control plan [16,17]. This study of cancer incidence during the societal transition in Addis Ababa aims to inform cancer control and serves as a baseline for assessing the effectiveness of future interventions.

2. Materials and methods

2.1. Setting of the population based cancer registry

The Addis Ababa City Cancer Registry is located in the Radiotherapy unit of the Addis Ababa University. The registry was established in September 2011 in collaboration with the Medical Faculty of Martin-Luther-University, Halle, Germany and Addis Ababa University, then the American Cancer Society and the World Health Organisation also stepped in. The Addis Ababa City Cancer Registry employs active data collection methods organized by the director, supervisor, two data collectors, a clerk and 22 focal persons (cancer registrars) at outpatient clinics, inpatient wards (internal medicine, Radiotherapy, Gynecology, Surgery, Pediatrics) as well as diagnostic laboratories.

The structured cancer registry questionnaire [18] was minimally adapted for the purpose of Addis Ababa City Cancer Registry. Demographic information, diagnostic findings and planned cancer therapies are collected. Due to the heterogeneity of the Ethiopian population, ethnic group was included.

2.2. Classification of cancers

Cancers were classified according to the third version of the International Classification of Disease for Oncology (ICD-O-3) [19].

2.3. Data collection

Data were collected and electronically entered and analyzed using CanReg5 software from the International Agency for Research on Cancer [20] and SPSS Version 24, IBM Corp. Edits were run on the data to check for implausible combinations of cancer sites and entities, and for duplicate cases. In this study, two consecutive years of data were used; the last update was performed in October 2016. The census data for Addis Ababa (comprising a population of 3,049.000 persons in 2011) was used for the calculation of the age-standardized rates [15].

2.4. Ethical approval

The implementation of the cancer registry was approved by the Addis Ababa Medical Faculty Institutional Review Board. Consent of all

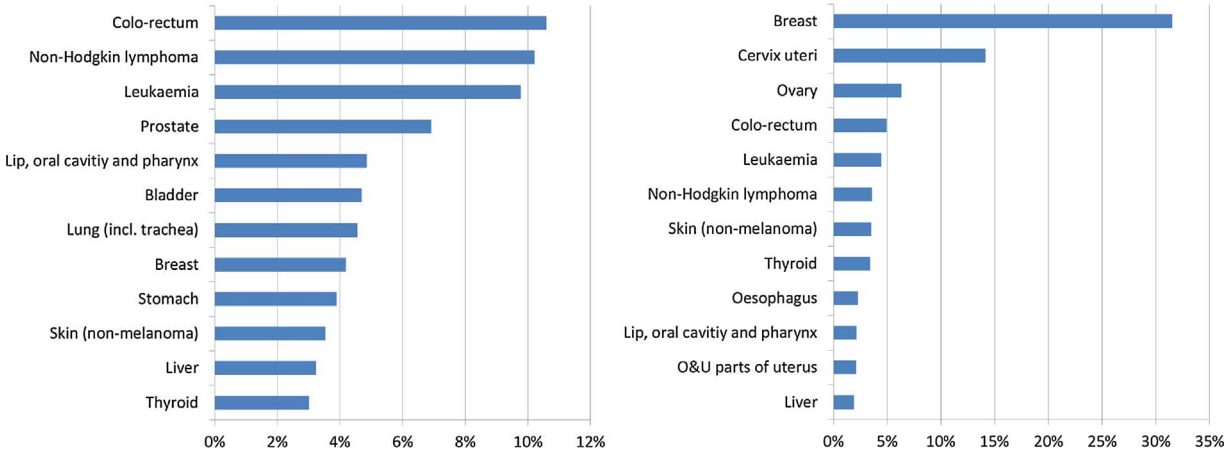

Fig. 2. Proportions of all cancers for the most common cancers in a) males and b) females.

administrators/directors of health institutions was given. Confidentiality was ensured.

3. Results

The population pyramid of Addis Ababa City is shown in Fig. 1; the population of the city, as for the country, was young, with a slight predominance of females.

The most common cancer sites among females were cancers of the breast (31.5%), cervix uteri (14.1%) and ovary (6.3%), while colorectal cancer (10.6%), non-Hodgkin lymphoma (10.2%), and prostate cancer (6.9%) were the most common among males (Fig. 2).

Of the total 4139 cancer cases recorded in 2012–2013, the majority were among females (68%), in the age group 30–49 years (40.8%) and among Amhara ethnicity (36.8%) (Table 1). About one third of patients did not disclose their ethnic group due to sensitive nature of the information. This was homogeneous throughout the collaborating facilities.

The age-standardized (Segi standard) incidence rates of cancers of the breast were 40.6, cervix uteri 21.5 and ovary 8.5 per 100,000 person years for females. The age-standardized incidence rates of cancers of the colorectum were 7.6, Non-Hodgkin Lymphoma 6.8 and prostate 6.4 per 100,000 person years for males in Addis Ababa Ethiopia (Table 2).

The age-specific incidence rates for breast cancer and colorectum are seen in Fig. 3.

Table 1
Demographic information of patients registered in Addis Ababa population-based Cancer Registry.

Patients 2012–13	Males (n = 1361)	%	Females (n = 2778)	%
Age groups				
< 10	62	4.6	32	1.2
10–19	58	4.3	57	2.1
20–29	127	9.3	268	9.6
30–39	185	13.6	585	21.1
40–49	212	15.6	546	19.7
50–59	237	17.4	601	21.6
60–69	257	18.9	427	15.4
70+	220	16.4	262	9.4
Ethnic group				
Amhara	385	28.3	1022	36.8
Oromo	175	12.9	367	13.2
Gurage	115	8.4	249	9.0
Tigre	94	6.9	134	4.8
Somalie	62	4.6	39	1.4
Other	51	3.7	88	3.2
Unkown	479	35.2	879	31.6

4. Discussion

4.1. Main findings

The Addis Ababa City Cancer Registry was the first population-based cancer registry providing data that served to inform cancer control and cancer research in Ethiopia. The age standardized rates per 100,000 of 136 for females and 70 for males were in line with rates reported from neighboring, long-standing registries such as Kenia (more Kaposi and prostate cancer in males) reporting 196 and 167 and Sudan (less cervical cancers in females) reporting 91 and 92 for females and males respectively. In Addis Ababa, 68% of the registered cases were in females, consistent to a higher burden in females observed in many population-based African cancer registries [7,21,22]. In females, cancer of the breast was the most commonly diagnosed cancer followed by cancer of the cervix uteri and the ovary. Given the low number of cases per entity, there were no major differences observed between the ethnic groups.

4.2. Colorectal and prostate cancer in males

Interestingly, in males, colorectal cancer was the leading cancer, followed by prostate cancer. The predominance of colorectal cancer in males was an unexpected finding and appears a unique observation when one examines cancer profiles from other registries in sub Saharan Africa. Most sub Saharan countries reported prostate cancers as leading cancer in males. The West African countries reported liver cancer and the South-East African countries reported Kaposi Sarkoma as leading cancer in males. There were unique leading cancers of the stomach in Mali and esophageal cancer in Botswana (data 2012) [7]. This suggested there were unique risk factors for colorectal cancer in Ethiopia relative to other countries on the continent. Equally, the other male cancer incidence rates appeared lower than in other African countries. Incidence rates of the disease in young males in Addis Ababa differed especially in the older age groups compared to European countries e.g. in Germany the incidence rates in males age 45–49 years was about 25/100,000 compared to 9/100,000 in the same age-group in the Ethiopian capital; in contrast the rates at older age-groups were 10-fold higher in Germany.

Established risk factors for colorectal cancer are alcohol consumption, cigarette smoking, obesity and meat consumption [23]. Also, a lack of micronutrients or fiber in food is reported as risk factors for colorectal cancer in some but not all studies [24]. Conversely, a Mediterranean diet (olive oil, vegetables, fruits, legumes, cereals, fish and a moderate intake of red wine during meals) has been shown to reduce risk. Possibly, there were some components in the Ethiopian diet compared to other African countries which may have increased the risk

Table 2
Cancer sites showing crude and age-standardized incidence rates (ASR) per 100, 000.

Cases 2012–2013		Males				Females			
	ICD 10	n	%	crude	ASR	N	%	crude	ASR
Lip. oral cavitiy and pharynx	C00-14	66	4.8	2.1	3.5	60	2.2	1.9	2.9
Oesophagus	C15	38	2.8	1.3	2.3	63	2.3	2	3.8
Stomach	C16	53	3.9	1.4	3.1	45	1.6	1.4	2.6
Colorectum	C18-20	144	10.6	5	7.6	137	4.9	4.3	7
Anus	C21	7	0.5	0.2	0.3	8	0.3	0.3	0.3
Liver	C22	44	3.2	1.5	2.5	53	1.9	1.7	3
Larynx	C32	11	0.8	0.4	0.7	1	0.0	0	0.1
Lung (incl. trachea)	C33-34	62	4.6	2.1	3.7	45	1.6	1.4	2.7
Skin (non-melanoma)	C44	48	3.5	1.7	2.6	98	3.5	3.1	4.9
Kaposi sarcoma	C46	18	1.3	0.6	0.6	14	0.5	0.4	0.5
Breast	C50	57	4.2	2	3.2	876	31.5	27.4	40.6
Vulva	C51					31	1.1	1	1.5
Cervix uteri	C53					393	14.1	12.3	21.5
O&U part of uterus	C54-55					58	2.1	1.8	2.9
Ovary	C56					175	6.3	5.5	8.5
Prostate	C61	94	6.9	3.2	6.4				
Kidney etc.	C64-66	25	1.8	0.9	1.4	39	1.4	1.2	2
Bladder	C67	64	4.7	2.2	3.9	26	0.9	0.8	1.5
Eye	C69	18	1.3	0.6	0.8	19	0.7	0.6	0.8
Brain. central nervous system	C70-72	30	2.2	1	1.2	23	0.8	0.7	1
Thyroid	C73	41	3.0	1.4	2	95	3.4	3	4.2
Hodgkin's lymphoma	C81	29	2.1	1	0.9	19	0.7	0.6	0.6
Non-Hodgkin's lymphoma	C82-88, C96	139	10.2	4.8	6.8	99	3.6	3.1	4.5
Leukaemia	C91-95	133	9.8	4.5	5.9	124	4.5	3.9	5.6
Other & unspecified		240	17.6	8.1	11.6	277	10.0	8.9	13.2
All sites		1361	100.0	46.0	70.7	2778	100.0	87.0	136.2

of colorectal cancer (e.g. eating red meat, lack of fruit and vegetables and therefore lack of vitamins), even though traditional foods such as the common bread ("injera") are high in possibly protective fiber and contains legumes [25,26]. The high numbers of the colorectal cancer may suggest possible associations with the known widespread prevalence of *helicobacter pylori* in Africa [27].

4.3. Breast and cervical cancer in females

Female breast and cervical cancer were the leading cancers among females based on findings from other cancer registries in Sub-Saharan Africa [28]. Trends in breast cancer incidence from longstanding registries in Uganda and Zimbabwe showed an annual increase of 3.6% and 4.9% during the last 20 years [21,29]. Some reproductive factors may have been responsible for the high incidence of breast cancer in Addis Ababa. Compared to the country-wide total fertility rate of 5.5 children, it was only 1.5 in Addis Ababa [15]. The decline of incidence seen among the older age group is probably a cohort effect. The decline around age 70 should be interpreted with caution since there are only 25 cases reported in that age group (Fig. 3). Additionally the underlying population in the old and very old age group has possibly high uncertainty about their own age. Reports elsewhere suggested that various risk factors including the eating of foods low in fiber, and high in fats and calories, an inactive lifestyle, smoking, and excess alcohol consumption were contributing factors to the increasing cancer burden especially e.g. for female breast cancer [30]. Espey and colleagues (2007) associated the occurrence of all cancer with diets, westernized life style, urbanization, industrialization and stressed social factors [31,32]. As with most population-based cancer registries, variables that directly measure associated risk factors, such as those mentioned above, were not routinely collected in Addis Ababa. Studies elsewhere have shown that the cancer burden is increasingly elevated in transitioning societies with westernized lifestyles, obesity and reproductive factors among the determinants [33,34]. It should be noted that patients often presented at late stage within the health system in Ethiopia [35] which can effect presence of risk factors inquired during presentation.

The occurrence of non-Hodgkin lymphoma among the most common cancers may reflect its association with oncogenic viral infection [36]. This high occurrence was also seen in the Addis Ababa registry. Cervical cancer, as the second most common cancer at the

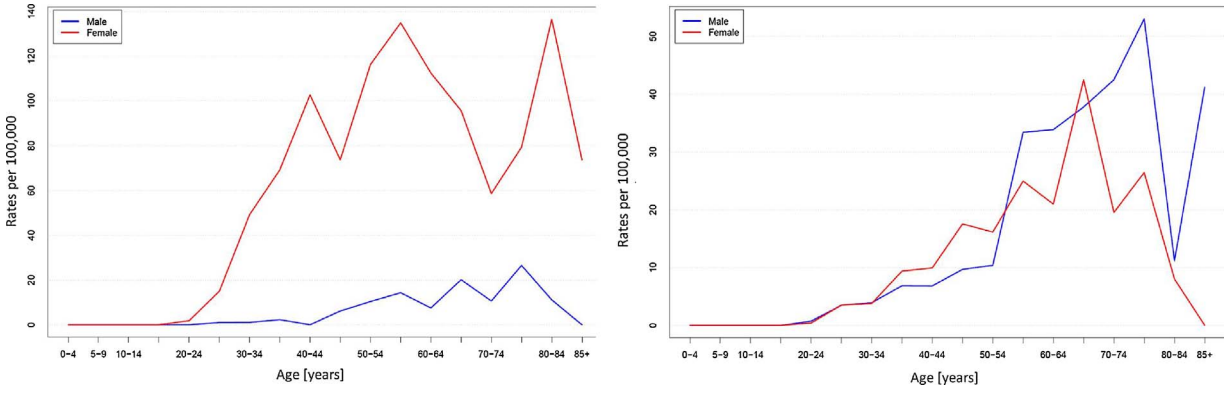

Fig. 3. Age-specific incidence rates of a) breast cancer and b) colorectal cancer per 100.000 in 2012–2013.

registry, causes high levels of suffering and provokes due attention for the need for national vaccination to prevent high incidence and mortality rates from this preventable cancer. The HIV prevalence in Ethiopia was estimated to be low with an overall adult prevalence of 2.4%, with a prevalence of 7.7% in urban areas [37], and therefore, the proportion of Kaposi sarcoma was probably not high. Since there was no cervical cancer screening in Ethiopia, an ASR of 21.5 for cervical cancer may have represented the reality; this rate contrasts with the 40.1/100,000 in Kenya (ASR), a country with higher HIV prevalence and 7.8/100,000 in Sudan, a country with lower HIV prevalence [28]. Since the government is recently planning to roll-out an human papilloma virus vaccination program for the general population aged between 9 and 13, changes in incidence over time will show the success of this program.

4.4. Limitations

There was a substantial chance of under-registration in the Addis Ababa cancer registry, similar to most registres in Africa, for several reasons. First, not all facilities treating patients in the city registered and reported cancer cases to the registry [38]. However, only few small facilities were not collaborating. Second, a substantial number of cancer patients may have never been seen in the formal health system [39]. Our method of data collection by definition excluded patients who never visit the formal health institutions, but we assume that cancer patients in Addis were more likely to visit a health facility compared to other parts of the country. In future, more emphasis will be made to also include clinically suspicious cases without histology by providing training to the data collectors. Other improvement is expected by a continuous increase in awareness of the Addis Ababa population. Third, some cancer sites were likely to be misclassified due to limitations of the services the health institutions provided [40]. Neurosurgery, lung surgery and abdominal surgery were very limited in Addis Ababa. Therefore, neural cancer or pancreatic cancers might not have been diagnosed, and lung cancer may have been misclassified as tuberculosis. Additionally, differential diagnoses of hematologic malignancies may have been possible given a lack of immunohistochemistry in Addis Ababa leading to an underestimate of the number of cases at the registry. Fourth, registering prevalent cases which were actually diagnosed in previous years was unavoidable in the first years of the registry [8]. Later such recurrent cases could be found by an automatic check for entry of the same name in previous years.

5. Conclusions

In conclusion, this study indicated that cancer is indeed a major health problem in Addis Ababa. Colorectal and breast cancer were most common in males and females respectively. The overall rates were still low compared to developed countries and not dissimilar to rates in other African countries. Females accounted for two-thirds of the cancer burden, largely due to the high rates of breast and cervical cancer. The proportion of colorectal cancer in males was higher than other countries, however. As seen in neighboring countries, cancer incidence rates are expected to increase with the major changes in unhealthy lifestyle factors underway. The ongoing cancer registration system in Addis Ababa will monitor these rates and the effects of interventions, as part of the national cancer control efforts in Ethiopia.

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Collection and/or assembly of data Genebo Timotewos, Asmare Solomon, Bekele Ayalnesh, Hailemariam Dagnechew, Wondatir Bireda.

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Conflicts of interest

None.

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Selbstständigkeitserklärung

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

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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.

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