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Clinical and demographic characteristics of cervical cancer patients presenting at Parirenyatwa Hospital, Zimbabwe

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Abstract

Cervical cancer is the leading cause of cancer deaths in women in Africa, predominately due to late diagnosis. This study aims to identify risk factors, potential prognostic indicators, and optimal treatment modalities for Zimbabwean cervical cancer patients. Medical records for 1063 cervical cancer patients were reviewed for sociodemographic, clinical, treatment, and response data. All data were analysed using SPSS version 25. More than half of the cohort was pre-menopausal (63%) with low (2%) history of cervical cancer screening. Schistosoma ova were observed in 2.4% of the tumour specimens. More than 50% were diagnosed at stage 3 and later, with a high frequency of comorbidities (~68%). This study highlights a need for improving screening education and uptake in Zimbabwe. Moreover, the current data provides a dataset for understanding cervical cancer pathogenesis and treatment responses in an African cohort. *(Afr J Reprod Health 2021; 25[6]: 99-109).*

Keywords: Clinicopathological profile, black African, cervical cancer, chemotherapy, Zimbabwe

Résumé

Le cancer du col de l'utérus est la principale cause de décès par cancer chez les femmes en Afrique, principalement en raison d'un diagnostic tardif. Cette étude vise à identifier les facteurs de risque, les indicateurs pronostiques potentiels et les modalités de traitement optimales pour les patientes zimbabwéennes atteintes d'un cancer du col de l'utérus. Les dossiers médicaux de 1063 patientes atteintes d'un cancer du col de l'utérus ont été examinés pour les données sociodémographiques, cliniques, de traitement et de réponse. Toutes les données ont été analysées à l'aide de SPSS version 25. Plus de la moitié de la cohorte était pré-ménopausée (63 %) avec de faibles (2 %) antécédents de dépistage du cancer du col de l'utérus. Des ovules de Schistosoma ont été observés dans 2,4 % des échantillons de tumeur. Plus de 50% ont été diagnostiqués au stade 3 et plus tard, avec une fréquence élevée de comorbidités (~68%). Cette étude met en évidence la nécessité d'améliorer l'éducation et l'adoption du dépistage au Zimbabwe. De plus, les données actuelles fournissent un ensemble de données pour comprendre la pathogenèse du cancer du col de l'utérus et les réponses au traitement dans une cohorte africaine. *(Afr J Reprod Health 2021; 25[6]: 99-109).*

Mots-clés: Profil clinicopathologique, noir Africain, cancer du col de l'utérus, chimiothérapie, Zimbabwe

Introduction

Cervical cancer is a major public health complication, especially in low- and middle-income countries where most of the global new cases (84%) and deaths (87%) are reported every year[1,2]. Sub-Saharan Africa (SSA) is defined as the global hotspot for cervical cancer, contributing to at least 25% of the regional deaths[3-5]. The Zimbabwe National Cancer Registry shows that cervical cancer is amongst the most common malignancies in the country, accounting for one in three new cancer cases (~2500) annually. As a consequence of late diagnosis and poor prognosis at presentation, about 64% of affected women in Zimbabwe succumb to cervical cancer-related illness[6-8]. Other

factors contributing to high morbidity and mortality include poor health-seeking practices; paltry remuneration of healthcare workers; low implementation of preventive and screening methods; and lack of man-power[9]. In addition, pathology services, which are key for cancer diagnosis and staging, are scarce and inequitable in LMICs, further exacerbating treatment delays and poor prognosis that translate to high mortality[10-11].

Interaction of the causative agent of cervical cancer, human papillomavirus (HPV), with biological, genetic, social, and economic factors, influences cervical carcinogenesis[9]. Host genetic composition, compromised immunity, environment, alcohol consumption, smoking, multiparity, sociocultural practices, and inflammation of the cervix induced by biological agents such as Schistosoma have been previously established as notable cervical cancer risk factors[10-13]. Emerging evidence explicates the role of the aforementioned risk factors on the clinical and pathological presentation of cervical cancer, as well as prognosis. However, cervical cancer clinicopathology profiles are heterogeneous between populations, on account of geopolitical and socioeconomic climate diversity[13-20]. Therefore, clinicopathological data can be useful to describe population-specific characteristics of cervical cancer, that can be harnessed to develop tailored policies and guidelines for ameliorated screening, diagnosis and prognosis.

Despite the wealth of data on cervical cancer clinicopathology in different populations, there are limited studies to describe Zimbabwean populations. Similar to other populations, poor survival and drug-induced toxicities have also been associated with low socioeconomic status and unresectable disease in Zimbabwe[21-24]. However, studies describing clinical factors such as behavioural and social practices that can ascribe risk to cervical cancer are limited. Furthermore, how common presenting symptoms may be utilised to develop local-specific educational tools for screening and early diagnosis also remains unclear. Early diagnosis is very important in Zimbabwe, due to the high prevalence of comorbidities such as HIV which exacerbate severe adverse reactions to anti-cancer therapy[25-27]. Thus, clinicopathological data are also fundamental to highlight circumscribed trends for diseases and how their management strategies can adversely affect patients, making them indispensable for future research and the advancement of patient care.

Methods

The present study aims to describe risk factors, potential prognostic indicators and optimal local treatment modalities for cervical cancer in a Zimbabwean cohort. As a secondary objective, the study aimed to evaluate possible relationships among clinical, demographic, and pathological information for Zimbabwean cervical cancer patients.

The study reviewed records for cervical cancer patients who were receiving care at the Parirenyatwa Group of Hospitals Radiotherapy and Chemotherapy Centre (RTC)[28]. All human health research procedures were per the Helsinki declaration of 2013. Ethical approval was obtained from the University of Zimbabwe College of Health Sciences and Parirenyatwa Group of Hospitals Joint Research Ethics Committee (412/16), Medical Research Council of Zimbabwe (A/2153), University of Cape Town Research Ethics Committee and Research Council of Zimbabwe (No: 03351).

The cervical cancer records were identified through the RTC registry and corresponding patient hospital numbers were employed to identify patient files. To be considered an eligible study participant, a record of confirmed cervical cancer diagnosis was obligatory in the patient file. Patient records excluded from this study were inaccessible, or were accessible but with insufficient clinical and demographic information. The requirement of informed consent from patients was waived because of the retrospective nature in which the patient records were to be reviewed.

The clinical and demographic information was extracted from paper-based patient files onto standardized case report forms. To maintain confidentiality and ensure research data could not be traced back to the patient, all study participants were assigned unique study identifiers. The collected participant data included age at diagnosis, race, place of permanent residency (rural/urban), body mass index (BMI) at diagnosis, co-morbidities, history of cervical cancer screening, personal and family history of cancer. Sexual, as well as obstetrics and gynecology histories, were recorded including the age of menarche, coitarche

(sexual debut), first conception age; history of genital warts or other sexually transmitted infections, history of contraceptive use, number of sexual partners, parity and history of miscarriages. Lifestyle-related risk factors such as a history of alcohol consumption and smoking were also noted for analysis. In addition, tumour characteristics, histological staging, treatment methods, and treatment outcomes were also noted.

Data analysis

The IBM SPSS version 25 was used to conduct statistical analysis. Descriptive statistics were computed for the demographic factors and all variables were scaled to determine frequencies, proportions, means, medians, and standard deviations. Comparisons and associations were done using independent t-test, cross-tabulation, and one-way ANOVA. The measure of significance was $p<0.05$. For multiple category comparisons, a one-way ANOVA test was conducted for each variable and each variable had to satisfy both the Tukey's and Games-Howell tests. Tests of homogeneity of variances, robust test of equality and the means plot were also conducted.

Results

Patient demographic characteristics

During the 2012-2017 period, a total of 2019 cervical cancer patients registered in the RTC registry, however, only 1063 cervical cancer records satisfied the present study's inclusion parameters. The mean (±SD, range) age of this cohort was 52 years (±13.05, 17–101). The least frequent age group was <35 years (74; 7%), while the highest burden was in the 36-55 (573; 54%) age range. One-fifth of the cohort were residing in rural areas. The mean BMI was 36.8±19.5kg/m^2. High HIV prevalence (40.7%) was recorded, and nearly 90% of the HIV-positive participants were on antiretroviral therapy (ART) (Table 1).

Cervical cancer risk factors

The median ages (range) for sexual debut, menarche, menopause, and first pregnancy were, 18 (15-28), 16.5 (10-23) and 56 (44-68), and 19 (16-37) years, respectively (Table 1). Frequencies of nulliparity, primiparity and multiparity were: 1.7% (n=18), 2.2% (n=30) and 73.8% (n=785), respectively. More than 20% of the cohort had a history of 4 pregnancies. Fifteen women (1.4%) had a history of miscarriages or stillbirths. A total of 174 (16.4%) participants had a history of venereal disease, and 27 (2.5%) of them had genital warts. One participant stated they had never engaged in sexual activity in their lifetime (0 sexual partners). History of prior cancer diagnosis was low (<1%), while nearly 15% of participants had a positive history of cancer in the family. The most common reported familial cancers included cervical (37%) and breast (12%) cancers. History of cervical cancer screening was confirmed in a paltry 2%, and the rest (i.e. 98%) received their first cervical cancer screening as part of the diagnosis.

Table 1: Demographic characteristics and risk factors of cervical cancer patients

Characteristic	Mean ±SD (range)
Mean age ± SD	52 ± 13.05
Mean BMI ± SD	36.8 ± 19.47
Median Age at sexual debut (range)	18 (15-28)
Median Age of menarche (range)	16.5 (10 - 23)
Median Age of first pregnancy (range)	19 (16 - 37)
Median Parity (range)	8 (0– 17)
	n (%) out of 1063
Rural residence: (n=657)	225 (21.0)
Positive HIV status	433 (41.0)
Marital status (n=896)	
Single or never married	52 (5.0)
Married or widowed	844 (80.0)
Parity: (n=825)	
0	18 (2.2)
>1	807 (97.8)
History of miscarriage	15 (1.4)
History of STI infection	175 (16.4)
Number of sexual partners (n= 643)	
0-3	596 (92.7)
>4	47 (7.3)
Menopausal status	
Premenopausal	670 (63.0)
Postmenopausal	394 (34.2)
Prior history of cancer	6 (0.6)
Family History of cancer	155 (14.6)
Cervical cancer screening before diagnosis	21 (2.0)
Tobacco smoking/ snuffing	54 (5.1)
Alcohol consumption (n=811)	174 (21.5)
Polygamous marriage	24 (2.3)
History of herbal medicine	45 (4.2)

Key: BMI=body mass index, ART=antiretroviral therapy *NHL= non-Hodgkin's lymphoma ** CRC= colorectal cancer

Table 2: Symptomatic factors of cervical cancer patients at presentation

Symptoms	N (%)
Common symptoms (n= 1063)	
Inter-menstrual or post coital bleeding	540 (50.8)
Post-menopausal pelvic bleeding	329 (31.0)
Aberrant pelvic discharge	890 (83.7)
Foul smelling vaginal discharge	622 (58.5)
General systems complications	326 (30.7)
Respiratory Complications	114 (10.7)
Gastro intestinal/urinary Complications	303 (28.5)
Central Nervous System Complications	476 (45.0)
Rectovaginal Complications	58 (5.50)
Other (n= 30)	
Cardiomegaly	7 (23.0)
Audiometry[a]	23 (77.0)
Comorbidities (n=719)	
Cardiovascular Disease	433 (60.2)
Diabetes Mellitus	132 (18.4)
Renal Disease	55 (7.60)
Other	71 (9.90)

a- Audiometry = Hearing loss n=6; Tinnitus n=5; ear discharge n= 12

A total of 54 (5.1%) participants had a history of tobacco use and alcohol consumption was recorded in 21.5% of the participants. Only 3.7% (n=39) participants were reported to be physically active. Polygamous marriages were recorded in 2.3% (n=24) of this cohort. Nearly 5% (n=45) participants, had a history of vaginal insertions or douching with herbal medicines, either for cultural purposes or to remedy cervical cancer. Other unconventional remedies recorded included vaginal insertion of povidone iodine antiseptic ointment (Betadine®), which was observed in one participant's record.

Presenting signs and symptoms, as well as participant comorbidities

Presenting signs and symptoms observed in this cohort are described in Table 2. Most of the cervical cancer patients (99.3%) presented with symptoms. Common presenting symptoms included pelvic discharge (83.7%) characterized by a foul smell (58.5%), inter-menstrual/contact bleeding (50.8%) and post-menopausal pelvic bleeding (31%). On examination, patients also presented with complications in the central nervous (45%), gastrointestinal/urinary (29%), respiratory (11%) and rectovaginal (5.5%) systems. Comorbid conditions were recorded in 719 (67.6%) of the participants. The most common comorbidity was HIV (432; 60.2%) followed by cardiovascular disease (hypertension and hypotension) (132; 18.4%), diabetes mellitus (55; 7.6%) renal disease (71; 9.9%) and other (29; 4%).

Cervical cancer tumour characteristics and treatment

Squamous cell carcinoma (88.4%) was the most prevalent cervical cancer histological type, followed by adenocarcinoma (6.3%) (Table 3). Further histopathological examinations showed the presence of Schistosoma ova in 25 (2.4%) of the tumour biopsy specimens. For the patient records with available data, 25% had tumours <5cm in diameter and 20% were >5cm. At diagnosis, 54.1% of the tumours were on clinical stage 3, followed by stage 2 (31.9%). Parametrial involvement was recorded in 47% of patients and metastasis was confirmed in 8.5% of the patients.

The treating centre focuses on chemotherapy and radiotherapy thus, it was not surprising that chemoradiotherapy (74.5%) was the most common treatment modality (Table 3). Patient records showed a high remission rate (60.5%), living disease-free at the 12 months check-up, while 3.3% had relapsed within the same period. In 14.4% of participants, disease progression was recorded leading to referral for hospice services. During treatment, 7.2% of the participants stopped attending the clinic for follow-ups. A quarter of the individuals that completed were lost to follow-up at the 12-month check-up, and at this time-point, 20% were confirmed to be deceased. However, data on date and cause of death were not readily accessible for further analyses.

At the 12-month follow-up, 255 (24%) women experienced treatment-induced toxicities. The most common treatment-related toxicities were deep vein thrombosis (26%), followed by peripheral neuropathy (25.5%), vesicovaginal fistula (15%) and emesis (15%). In 5% (n= 53) cases, the adverse reactions were severe to the extent that therapy was discontinued. A total of 38 (15%) participants presented with single treatment-induced toxicity, while, 64 (25%) presented with two treatment-induced toxicities and 153 (60%) presented with >3 toxicities following anti-cancer therapy.

Table 3: Characteristics of tumour, treatment modalities, and response to therapy

Characteristic of tumour	N (%)
Tumour Histology (n= 1063)	
Squamous cell carcinoma (SCC)	940 (88.4)
Adenocarcinoma (ADC)	66 (6.3)
*Other	27 (2.5)
Schistosoma ova	25 (2.4)
Size (n= 478)	
<5cm	266 (25.0)
>5cm	212 (20.0)
Staging	
1	39 (3.7)
2	339 (31.9)
3	575 (54.1)
4	104(9.7)
Parametrial involvement	499 (47.0)
Metastasis (n= 393)	
No	303 (28.5)
Yes	90 (8.5)
Metastatic sites (n= 90):	
Bladder/ bladder wall	59 (65.0)
Ovary, Endometrium or Vulvar	27 (30.0)
Other	4 (5.0)
Treatment Modality (n= 719)	
Chemotherapy (Cisplatin or + 5 Fluorouracil/ Carboplatin/ Paclitaxel)	58 (8.0)
Radiotherapy (Brachytherapy or External Beam Radiation)	116 (16.1)
Chemoradiotherapy	536 (74.5)
Hysterectomy + Chemoradiotherapy	9 (1.4)
Treatment Response (n= 719)	
Remission (Disease-free survival)	435 (60.5)
Relapse	23 (3.3)
Deceased	144 (20.0)
Disease Progression	104 (14.4)
Defaulted treatment (n= 199)	
Default due to lack of funds	94 (47.2)
Default due to denial of diagnosis	105 (52.8)
Treatment-related toxicities (n= 255)	
DVT[b]	66 (26.0)
VVF[c]	38 (15.0)
Emesis	38 (15.0)
Renal failure	31 (12.0)
Peripheral neuropathy (lower limb pain; parasthesia)	65 (25.5)
Other	69 (27.0)
Loss to follow up (n= 1063)	344 (32.4)

a Other= Adenosquamous cell carcinoma (ADS) n= 24; Sarcoma n= 3; b DVT= deep vein thrombosis; c VVF= vesicovaginal fistula

Association of clinical characteristics

A positive association between the type of treatment and drug-related toxicities (p=0.007) was determined. There was a higher frequency of patients receiving chemoradiotherapy, and correspondingly those who experienced treatment-induced toxicities. Gastro- intestinal/-urinary complications were the most common toxicities developed in radiotherapy-based modalities i.e. radiotherapy alone (12; 3.6%) or in combination with chemotherapy (chemoradiotherapy) (60; 18%). Central nervous system-related complications were more common in participants who had received chemotherapy-based treatment namely chemoradiotherapy (60; 18%) and chemotherapy alone (24; 7.2%) (p=0.04). These CNS-related toxicities were mainly peripheral neuropathy (lower limb pain and paresthesia).

Discussion

Cervical cancer is a complex disease that is driven by the interplay of biological, environmental, socioeconomic, cultural, and geopolitical factors. However, in most LMICs, where there is significant diversity, the impact of these risk factors on carcinogenesis in the cervix is not well understood. It is, therefore, difficult to establish tailored guidelines for the assessment and management of patients. The present study identifies risk factors, potential prognostic indicators and describes optimal local treatment modalities for cervical cancer in Zimbabwe.

In SSA, nearly 70% of cervical cancer cases are diagnosed among patients from rural areas[25,29]. This study observes rural residency in only 21% of the cohort. Our findings may be reflective of the centralized oncology facilities in urban areas in Zimbabwe, resulting in rural patients attending treatment at urban oncology facilities. Consequently, these patients may use urban addresses, which are inadvertently captured as the respective permanent residence.

The mean age for the present cohort was 52 ±13.1years, resonating with previous studies on cervical cancer in Zimbabwe[23-25,27,30]. Our study further confirms the high prevalence (63%) of cervical cancer in premenopausal women as reported from studies among South African (68%) and Bangladeshi women (~62%)[28,29,31-34]. Pathophysiological changes occurring in pre-menopausal hormone-regulating episodes such as menstruation, pregnancy and the prolonged use of oral contraceptives can collectively induce chronic inflammation and lower immunity[33]. Chronic inflammation and compromised immunity perpetuate favourable microenvironments for HPV

persistence and carcinogenesis. There is some data on African populations reporting on a higher frequency of cervical cancer among post-menopausal women, which may be a result of the multi-aetiological nature of cervical cancer.

Although the age of sexual debut reported in our study data was typical to the Demographic and Health Surveys data (19 years), it is important to note that in India and other countries in SSA, marriage in adolescence and by default, early sexual debut, is common and a significant contributor for HPV acquisition and therefore cervical cancer[17,35-36]. Furthermore, various studies have reported on the effects of parity (number of times someone has carried full-term pregnancies), where multiparity is highly associated with increased risk of HPV acquisition and persistence when compared to nulliparity[17,37-38]. This points to the possible role of hormonal activity in the pregnancy cycles to establish conducive microenvironment for HPV persistence and tumorigenesis[17,37-38]. Previous studies conducted on Zimbabwean women show that multiparity conferred a nearly 2 fold risk of cervical cancer[39]. Although risk was not quantified in the present study, a mean parity of 4 that is comparatively higher than the global average parity of 2.5 was observed in the present study, translating to higher perceived risk[40].

In addition to hormonal pathophysiology, infectious agents such as schistosomiasis can alter the reproductive homeostatic balance, thereby promoting carcinogenesis. We report here a 2.4% prevalence of schistosomiasis in the cervical cancer tumour biopsies. The current study confirms earlier observations among Togolese (1.8%), Zambian (34%) women, as well as in case reports from South African and Angolan women, where Schistosoma ova were detectable in the histopathological analyses[41-44]. Female genital schistosomiasis is associated with immune-suppression, increased risk of HPV/HIV infection and acquisition[44-47]. A previous study conducted among Zimbabwean women showed schistosomiasis-induced high-grade squamous intraepithelial neoplasia, with no evidence of HPV, prompting the necessity of investigating the relationship between schistosoma and cervical cancer in Zimbabwean populations[48].

Tobacco smoke and alcohol consumption have also been shown to pose a cumulative risk in HPV persistence, leading to suppression of immunity and shortened progression-free survival[49-51]. In this study, we recorded a 5.1% and 21.5% incidence of tobacco smoking and alcohol consumption, respectively. Due to westernisation and modernisation of the Zimbabwean society, tobacco smoking and alcohol consumption are on the rise. The potential impacts of these social changes range widely concerning cervical cancer, for example, augmenting perceived risks of disease acquisition, interfering with the management of patients, and diminishing patient prognosis.

Another factor that has been associated with an increased risk of developing cervical cancer is vaginal douching. The current study reports on 4.2% patient records with a history of using traditional and herbal vaginal douches. Vaginal douching deregulates the reproductive homeostatic balance, by stripping the normal vaginal flora. As a result, the reproductive tract is predisposed to sexually transmitted infections such as gonorrhoea, chlamydia and HPV[52-53].

Similar to other studies, we report on vaginal discharge (83.7%) and contact bleeding (50.8%), as the most common presenting symptoms[18,54]. As observed in most LMICs such as India (75%), more than half (63.8%) of the participants in this cohort presented with stage 3 cervical cancer, compounded with poor performance status and therefore, poor prognosis[18]. This could be driven by many factors, including the corresponding low history of cervical cancer screening (2%) observed in this cohort in comparison to the 100% screening recorded in Italy and Nordic countries[8]. Health-system-related barriers, or poor health-seeking behaviour as highlighted in our previous study[8] are significant barriers for cervical cancer screening in Zimbabwe[55].

Consistent with the disease burden in southern Africa, the most common comorbid condition was HIV. It is encouraging to note that 95% of the HIV-positive patients were on antiretroviral therapy, complying with the World Health Organisation's 90-90-90 strategy of testing, treating, and viral suppression. Thus, the effectiveness of both ART and chemotherapeutic drug intervention would depend on their interaction[56-59]. For example, combining antiretrovirals with anti-neoplastic drugs has been correlated with overlapping severe toxicities[59-62]. Our study shows that concurrent cisplatin-based

chemoradiotherapy was the most common treatment modality. Concurrent chemoradiotherapy has been previously described as the holy grail management for patients with good performance status, while radiotherapy alone was reserved for elderly or poorly patients that cannot tolerate chemotherapy[27,63]. Cisplatin chemotherapy is associated with a wide range of treatment-induced toxicities. One of the prevalent toxicities is peripheral neuropathy which is estimated to occur in 60% of patients receiving cisplatin[35]. Our study records peripheral neuropathy in 25.5% of the cohort. The onset of cisplatin-induced peripheral neuropathy is at cumulative doses higher than 300mg/m^2 and can be reversed by treatment cessation, but in most instances, is not reversible[64-67]. To avoid high cumulative cisplatin doses, and consequently, treatment induced toxicities, radiotherapy can be co-administered[64]. Therefore, the low prevalence observed in our cohort may be attributable to lower cisplatin doses administered concurrently with chemoradiotherapy, compared to individuals who were receiving cisplatin only. However, in low-resource settings where there is under-staffing, poor resources and overstretched facilities, screening for non-lethal treatment-induced toxicities such as peripheral neuropathy may not be offered as part of routine care, leading to many cases going undetected. In future, prospective studies to establish the prevalence of treatment-induced toxicities in cancer patients can be conducted, towards establishing optimal patient care.

Cervical cancer has been previously described as familial cancer, with heritability that ranges widely, between 22-64%[68-72]. The present study observes 37% of the cohort reported a positive history of familial cervical cancer, a finding which warrants future studies on the inheritability of cervical cancer in Zimbabwean women. Genomics is still a growing field in Zimbabwe, but as it grows, we anticipate expansive research on genetic susceptibility and familial clustering of diseases such as cervical cancer, which can be applied for pre-symptomatic testing and early administration of preventative measures, such as the HPV prophylactic vaccine.

According to our data, there was high loss to follow up and treatment non-completion. Treatment defaulting is a resounding challenge especially in countries like Zimbabwe, where there is limited government assistance for chronic illnesses, and patients pay for healthcare out of pocket. Low socioeconomic status, compounded with lack of adequate education and centralized health facilities culminate in poor health-seeking behaviour, which may drive consumption of cheaper alternative remedies[8,27,73]. Furthermore, of the 2019 cervical cancer cases recorded in the RTC registry, 956 were excluded from analysis because patient files were missing or contained inadequate patient information. These challenges are seen in hospital settings that use paper-based patient medical records, such as the RTC. While paper-based patient records have reduced upfront costs, they can be time-consuming, susceptible to errors, insecure, unstructured and prone to loss or physical damage[74]. As medicine advances to a personalized approach, it is important for health care facilities such as RTC to adapt to electronic medical record-keeping, to ensure systematic patient data collection, which can be useful for research, disease surveillance, analyses of disease trends, and for improved translation into daily clinical practice.

There are, however, two main limitations of this study, (i) the study was conducted at one hospital facility, the Radiotherapy and Chemotherapy Centre, and (ii) generally poor information and record keeping in patients' medical files which resulted in the exclusion of ~50% of initially accessed files due to insufficient clinical and/or demographical data. Particularly, it was difficult to find information on dates or causes of death, limiting our ability and possibility of calculating mortality rates and hazards ratios. However, despite these limitations, this study adds to what is known about the unraveling clinicopathological factors that are observed in Zimbabwean cervical cancer patients.

Conclusion

This study presents clinicopathological data on Zimbabwean cervical cancer patients and can be used as an initial dataset for future work on the relationship between risk factors in optimizing therapy, cervical carcinogenesis and response to treatment. Our findings underscore the need to promote frequent cervical cancer screening in premenopausal women, and awareness campaigns to promote screening when aberrant vaginal discharge is observed. This data is a fundamental

step for the development of social, and culturally relevant educational materials that improve acceptance of preventive cervical cancer measures, as well as, identifying practices that aggravate the disease or improve treatment outcomes.

References

1. World Health Organisation. Cancer: Fact sheets. 2019. [Accessed online via:https://www.who.int/news-room/fact-sheets/detail/cancer] Accessed on 22 October 2019.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J. and Jemal A. Global cancer statistics. CA Cancer J. Clin 2015; 65: 87–108. https://www.ncbi.nlm.nih.gov/pubmed/25651787.
3. Mboumba Bouassa RS, Prazuck T, Lethu T, Meye JF and Belec L. Cervical cancer in sub-Saharan Africa: an emerging preventable disease associated with oncogenic human papillomavirus. Med Sante Trop 2017; 27(1): 16-22. https://www.ncbi.nlm.nih.gov/pubmed/28406406.
4. Johnson LG, Armstrong A, Joyce CM, Teitelman AM and Buttenheim AM. Implementation strategies to improve cervical cancer prevention in sub-Saharan Africa: A systematic review. Implementation Science 2018; 13(1): 28-46. https://www.ncbi.nlm.nih.gov/pubmed/29426344.
5. Jedy-Agba E, Joko WY, Liu B, Buziba NG, Borok M, Korir A, Masamba L, Manraj SS, Finesse A, Wabinga H, Somdyala N and Parkin DM. Trends in cervical cancer incidence in sub-Saharan Africa. BJC 2020; 123(1): 148-154. https://doi.org/10.1038/s41416-020-0831-9.
6. Johnson LG, Armstrong A, Joyce CM, Teitelman AM and Buttenheim AM. Implementation strategies to improve cervical cancer prevention in sub-Saharan Africa: A systematic review. Implementation Science 2018; 13(1): 28-46. https://www.ncbi.nlm.nih.gov/pubmed/29426344.
7. Chokunonga E, Borok MZ, Chirenje MZ, Makunike-Mutasa R, Ndlovhu N, Nyakabau AM and Vuma S. Pattern of cancer in Zimbabwe: Zimbabwe national cancer registry 2014 annual report. Ministry of Health and Child Care. 2015 [Accessed online via: https://www.globalgiving.org/pfil/40777/projdoc.pdf] Accessed on: 7 July 2020.
8. Kuguyo O, Matimba A, Tsikai N, Magwali T, Madziyire M, Gidiri M, Dandara C and Nhachi C. Cervical cancer in Zimbabwe: a situations analysis. Pan Afr Med J 2017; 27(215): 1-18. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5622829/.
9. Kassa RT. Risk factors associated with precancerous cervical lesion among women screened at Marie Stops Ethiopia, Adama town, Ethiopia 2017: a case control study. BMC Res Notes 2018; 11(1): 145-150. https://www.ncbi.nlm.nih.gov/pubmed/29463299.
10. Haileselassie W, Mirgissa K, ArayaSellasie M, Mulugeta T and Labisso WL. Challenges and opportunities in cancer diagnosis in Ethiopia: in depth exploration of practitioners' view. International Journal of Current Research 2017; 9(7): 54662-54668. https://www.journalcra.com/article/challenges-and-opportunities-cancer-diagnosis-ethiopia-depth-exploration-practitioners%E2%80%99%-view.
11. Gopal S, Wood WA, Lee SJ, Shea TC, Naresh KN, Kazembe PN, Casper C, Hesseling PB and Mitsuyasu RT. Meeting the challenge of hematologic malignancies in sub-Saharan Africa. Blood 2012; 119(22): 5078–5087. http://dx.doi.org/10.1182/blood-2012-02-387092.
12. Black E and Richmond R. Prevention of cervical cancer in sub-Saharan Africa: the advantages and challenges of HPV vaccination. Vaccines (Basel) 2018; 6(3): 61-69. https://www.ncbi.nlm.nih.gov/pubmed/30205561.
13. Cao L, Wen H, Feng Z, Han X and Wu X. Distinctive clinicopathologic characteristics and prognosis for different histologic subtypes of early cervical cancer. International Journal of Gynecological Cancer 2019; 29(8):1244-125. http://dx.doi.org/10.1136/ijgc-2019-000556.
14. Jain R, Nigam RK, Malik R and Jain P. Clinicopathological presentation of cervical cancer in Bhopal. Indian Journal of Medical and Paediatric Oncology 2019; 40(5): 33-37. https://www.ijmpo.org/article.asp?issn=0971-5851;year=2019;volume=40;issue=5;spage=33;epage=37;aulast=Jain.
15. Raju K, CV R and SR S. Clinicopathological correlation of invasive squamous cell carcinoma of uterine cervix: A cross-sectional study. Biomed Res. Ther. 2019; 6(11): 3443-3451. https://doi.org/10.15419/bmrat.v6i11.573.
16. Ikechebelu JI, Onyiaorah IV, Ugboaja JO, Anyiam DCD and Eleje GD. Clinicopathological analysis of cervical cancer seen in a tertiary health facility in Nnewi, South-East Nigeria. Journal of Obstetrics and Gynaecology 2010; 30(3). https://doi.org/10.3109/01443610903531394.
17. Afroj S, Banu MA, Sultana S, Jahan R, Rahman S and Begun N. Clinicopathological profile of cervical cancer patients attending in a specialised. J Dhaka Med Coll 2017; 26(2): 117-21. https://www.banglajol.info/index.php/JDMC/article/view/38826.
18. Shruthi PS, Kalyani R, Kai LJ and Narayanaswamy M. Clinicopathological correlation of cervical carcinoma: a tertiary based study. Asian Pac J Cancer Prev 2014; 15(4): 1671-4. https://www.ncbi.nlm.nih.gov/pubmed/24641387.
19. Kaur A, Chawla A, Manjari M. Incidence and Clinicopathological correlation of cervical cancer in a tertiary care center: a 5-year retrospective study. Curr Trends Diagn Treat 2019; 3(2): 64-67. https://www.ctdt.co.in/doi/CTDT/pdf/10.5005/jp-journals-10055-0078.
20. Rana MK, Singh K, Mahajan MK and Rana APS. Clinicopathological profile of cervical carcinoma: an experience of tertiary care cancer centre. Asian Pacific Journal of Cancer Care 2019; 4(3): 83-86.

https://doi.org/10.31557/APJCC.2019.4.3.83-86.
21. Kasule J. The pattern of gynaecological malignancy in Zimbabwe. East Afr Med J 1989; 66(6): 393-9. https://pubmed.ncbi.nlm.nih.gov/2791944/
22. Chirenje MZ, Rusakaniko S, Akino V and Mlingo M. A review of cervical cancer patients presenting in Harare and Parirenyatwa Hospitals in 1998. Centr Afr J Med 2000; 46(10): 264-7. https://pubmed.ncbi.nlm.nih.gov/11682933/.
23. Mushosho EY, Ndlovu N, Engel-Hills P and Wyrley-Birch B. Presentation patterns of invasive cancer of the cervix: results from Parirenyatwa Oncology and Radiotherapy Centre, Harare, Zimbabwe 1998-2010. Centr Afr J Med 2011;57(9-12): 43-9. https://pubmed.ncbi.nlm.nih.gov/24968662/
24. Ndlovu N and Kambarami R. Factors associated with tumour stage at presentation in invasive cervical cancer. Centr Afr J Med 2003; 49(9-10): 107-11 https://pubmed.ncbi.nlm.nih.gov/15298465/
25. Chirenje ZM. HIV and cancer of the cervix. Best Pract Res Clin Obstet Gynaecol 2005;19(2): 269-76. https://doi.org/10.1016/j.bpobgyn.2004.10.002.
26. Einstein MH, Ndlovu N, Lee J, Stier EA, Kotzen J, Garg M, Whitney K, Lensing SY, Tunmet M, Kadzatsa W, Palefsky J and Krown SE. Cisplatin and radiation therapy in HIV-positive women with locally advanced cervical cancer in sub-Saharan Africa: A phase II study of the AIDS malignancy consortium. Gynecol Oncol 2019; 153(1): 20-25 https://pubmed.ncbi.nlm.nih.gov/30773222/ .
27. Nyamhunga A, Ndlovu N, Kadzatsa W, Morse GD and Maponga CC. Chemoradiation in Stage IIIB cancer of the uterine cervix: A review of the Zimbabwean experience. JCO Global Oncology 2020; 6: 1554-1564. https://ascopubs.org/doi/full/10.1200/JGO.19.00412
28. Kuguyo O, Misi FD, Chibonda S, Matimba A, Nhachi C and Tsikai N. Pain management strategies among cervical cancer patients in Zimbabwe. Future Medicine: Pain Management 2021. [Accessed online via: https://www.futuremedicine.com/doi/full/10.2217/pmt-2020-0108]. Accessed on 18 August 2021.
29. Nejo YT, Olaleye DO and Odaibo GN. Prevalence and risk factors for genital human papillomavirus infections among women in Southwest Nigeria. Arch Basic Appl Med 2018; 6(1): 105-112. https://www.ncbi.nlm.nih.gov/pubmed/29905313.
30. Chokunonga E, Ramanakumar AV, Nyakabau AM, Borok MZ, Chirenje M, Sankila R and Parkin MD. Survival of cervix cancer patients in Harare, Zimbabwe, 1995-1997. Int J Cancer 2004; 109: 274-277. https://www.researchgate.net/publication/8897444.
31. Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. Estimates of worldwide burden of cancer in 2009: Globocan 2008. Int J Cancer 2010; 127(12): 2893-917. https://www.ncbi.nlm.nih.gov/pubmed/21351269.
32. Human Papillomavirus Information for Cancer Organization. Information on HPV and cancer for South Africa. [Accessed online via: https://hpvcentre.net/statistics/reports/ZAF.pdf] Accessed on 22 March 2020.
33. Ferdous J, Begum SA, Ferdous NE, Nahar Q, Khatum SF and Khatun S. Presentation of invasive cervical cancer in Bangladesh. BSMMUJ 2013; 8(1): 29-32. https://www.banglajol.info/index.php/BSMMUJ/article/view/29021.
34. Kennedy NT, Ikechukwu D and Goddy B. Risk factors and distribution of oncogenic strains of human papilloma virus in women presenting for cervical cancer screening in Port Harcourt, Nigeria. Pan Afr Med J 2016; 23:85. https://www.ncbi.nlm.nih.gov/pubmed/27222684.
35. Nessa A, Chowdhury SB, Fatima P, Sharif M and Azad AK. Cervical cancer screening program in Bangladesh. Bangladesh Journal of Obstetrics and Gynaecology 2020; 33(1): 63-73. https://doi.org/10.3329/bjog.v33i1.43550.
36. Kerry MLD, Mallick L and Allen C. Sexual and reproductive health in early and later adolescence: DHS data on youth age 10-19. DHS Comparative reports No. 45. [Accessed online via: https://dhsprogram.com/pubs/pdf/CR45/CR45.pdf] Accessed on 18 January 2021.
37. Bobdey S, Sathwara J, Jain A and Balasubramaniam G. Burden of cervical cancer and role of screening in India. Ind J Med 2016; 37(4): 278-85. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5234166/.
38. Ghosh M, Rodriguez-Garcia M and Wira CR. The immune system in menopause: pros and cons of hormone therapy. J Steroid Biochem Mol Biol 2013; [Accessed via: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3954964/] Accessed on: 25 October
39. Parkin DM, Vizcaino AP, Skinner ME and Ndhlovu A. Cancer patterns and risk factors in the African population of southwestern Zimbabwe, 1963-1977. Cancer Epidemiol Biomarkers Prev 1994; 3(7): 537-547. https://pubmed.ncbi.nlm.nih.gov/7827583/
40. Fadahunsi OO, Omoniyi-Esan GO, Banjo AA, Esimai OA, Osiagwu D, Clement F, Adeteye OV, Bejide RA and Iyiola S. Prevalence of High Risk oncogenic HPV types in cervical smears of women attending well women clinic in Ile-Ife. Gynaecol Obstet 2013; 3(6):1000185. https://www.longdom.org/open-access/prevalence-of-high-risk-oncogenic-human-papillomavirus-types-in-cervical-smears-of-women-attending-well-woman-clinic-in-ile-ife-nigeria-2161-0932.1000185.pdf.
41. Roser M. Fertility Rate. 2019 [Accessed online via: https://ourworldindata.org/fertility-rate]. Accessed on 5 Dec 2019.
42. Darre T, Aboubakari AS, N'Bortche BK, Bassowa A and Napo-Koura G. Association of Schistosomiasis with cervical cancer in Togo: the consequence of this association. Pathol Oncol Res 2019; 25(2): 807-808. https://www.ncbi.nlm.nih.gov/pubmed/29079966.
43. Mutengo MM, Mudenda V, Mwansa JC, Kaonga K, Sianongo S and Wamulume H. Presence of Schistomiasis in genital biopsies from patients at the university teaching Hospital in Lusaka, Zambia. Med J Zambia 2010; 26(3): 114–118. https://www.ajol.info/index.php/mjz/article/download/56075/44529.

44. Pillay P, Lieshout L, Taylor M, Sebitloane M, Zulu SG, Kleppa E, Roald B and Kjetland EF. Cervical cytology as a diagnostic tool for female genital schistosomiasis: correlation to cervical atypic and schistosoma polymerase chain raction. Cytojournal 2016; 13(10). https://www.ncbi.nlm.nih.gov/pubmed/27168759.
45. Toller A, Scopin AC, Apfei V, Pringezi KCK, Tso FK, Focchi GRA, Speck N and Ribalta J. An interesting finding in the uterine cervix: Schistosoma hematobium calcified eggs. Autos Case Rep 2015; 5(2): 41-44. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4584668/.
46. Savardekar LS, Balaiah D and Mali BN. Association of Schistosoma haematobium and human papillomavirus in cervical cancer: a case report. Acta Cytol 2010; 54(2): 205-8. https://www.ncbi.nlm.nih.gov/pubmed/20391981.
47. Mbah MLN, Poolman EM, Drain PK, Coffee MP, van der Werf MJ and Galvani AP. HIV and Schistosoma haematobium prevalences correlate in sub-Saharan Africa. Trop Med Int Health 2013; 18(10):1174-1179. https://www.ncbi.nlm.nih.gov/pubmed/23952297
48. Norseth HM, Ndhlovu PD, Kleppa E, Randrianasolo BS, Jourdan PM, Roald B, Holmen SD, Gundersen SG, Bagratee J, Onsrud M and Kjetland EF. The colposcopic atlas of schistosomiasis in the lower female genital tract based on studies in Malawi, Zimbabwe, Madagascar and South Africa. PLoS Negl Trop Dis 2014; 8(11): e3229. https://www.ncbi.nlm.nih.gov/pubmed/25412334
49. AVERT organization. HIV and AIDS in Zimbabwe. 2018. [Accessed online via: https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/zimbabwe] Accessed on: 21 Nov 2018.
50. Min KJ, Lee JK, Lee S and Kim MK. Alcohol consumption and viral load are synergistically associated with CIN1. PLoS One 2013; 8(8): e72142. https://www.ncbi.nlm.nih.gov/pubmed/23977233.
51. Cao S, Yang C, Gan Y and Lu Z. The Health Effects of Passive Smoking: An Overview of Systematic Reviews Based on Observational Epidemiological Evidence. PLoS One 2015; 10(10): e0139907. https://www.ncbi.nlm.nih.gov/pubmed/26440943
52. Kjetland EF, Ndhlovu PD, Mduluza T, Deschooleester V, Midzi N, Gomo E, Gwanzura L, Mason PR, Vermorken JB, Friis H, Gundersen SG and Baay MF. The effects of genital schistosoma haematobium on human papillomavirus and the development of cervical neoplasia after five years in a Zimbabwean population. Eur J Gynaecol Oncol 2010; 31(2): 169-73. https://www.ncbi.nlm.nih.gov/pubmed/20527233.
53. Martino JL and Vermund SH. Vaginal douching: evidence for risks or benefits to women's health. Epidemiol Rev 2008; 24(2): 109-24. https://www.ncbi.nlm.nih.gov/pubmed/12762087.
54. Suwannarurk K, Bhamarapravatana K, Kheolamai P, Thaweekul Y, Mairaing K, Poomtavorn Y and Pattaraararchachal J. Can self vaginal douching for high risk HPV screening replace or assist efficacy of cervical cancer screening?. Asian Pac J Cancer Prev 2010; 11(5): 1397-401. https://www.ncbi.nlm.nih.gov/pubmed/21198300
55. Gundrajakuppam L, Shanthi V and Rao NM. Clinicopathological correlation of cervical carcinoma by Pap smear. J Biosci Tech 2011; 2: 439-45.
56. Holman LL, Ran Y and Westin SN. Status of epilepticus associated with platinum chemotherapy in a patient with cervical cancer: a cancer report. BMC Cancer 2015; 15: 728. https://bmccancer.biomedcentral.com/articles/10.1186/s12885-015-1755-2.
57. Rudek MA, Flexner C and Ambinder RF. Use of anti-neoplastic agents in cancer patients with HIV/AIDS. Lancet Oncol 2010; 12(9): 905-12. https://www.ncbi.nlm.nih.gov/pubmed/21570912.
58. Berretta M, Caraglia M, Martellotta F, Zappavigna S, Lombardi A, Fierro C, Atripaldi L, Muto T, Valente D, Paoli PD, Tirelli U and Francia RD. Drug-drug interactions based on pharmacogenetics profile between highly active antiretroviral therapy and anti-neoplastic chemotherapy in cancer patients with HIV infection. Front Pharmacol 2016; 7(71): 1-17. https://europepmc.org/article/med/27065862.
59. Welz T, Wyen C and Hensel M. Drug interactions in the treatment of malignancy HIV-infected patients. Oncol Res Treat 2017; 40:120-7. https://www.karger.com/Article/Abstract/458443.
60. Xulu KR and Hosie MJ. HAART induced cell death in a cervical cancer cell line, HCS-2: a scanning electron microscopy study. J Microsc Ultrastruct 2017; 5(1): 39-48. https://www.ncbi.nlm.nih.gov/pubmed/30023236.
61. Pham PA and Flexner C. Emerging antiretroviral drugs interactions. Journal of antimicrobial chemotherapy 2010; 66(2): 235-9. https://www.ncbi.nlm.nih.gov/pubmed/21131695.
62. Makinson A, Pujol J, Moing VL, Peyriere H and Reynes J. Interactions between cytotoxic chemotherapy and antiretroviral treatment in human immune-deficiency virus-infected patients with lung cancer. Journal of Thoracic Oncology 2010; 5(4): 562-71. https://doi.org/10.1097/JTO.ob013e3181d3ccf2.
63. Srivastava K, Paul S, Chufal KS, Shamsunder SD, Lal P, Pant MC, Bhatt M, Singh S and Gupta R. Concurrent chemoradiation versus radiotherapy alone in cervical carcinoma: A randomized phase III trial. Asia Pac J Clin Oncol 2013; 9(3): 349-356. https://doi.org/10.1111/ajco.12078.
64. Amptoulach S and Tsavaris N. Neurotoxicity caused by the treatment with platinum analogues. Chemotherapy Research Practice 2011; 843019. https://doi.org/10.1155/2011/843019
65. Smith EM, Pang H, Cirrincione C, Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA 2013; 309(13): 1359–67. https://doi.org/10.1001/jama.2013.2813.

66. Gupta R and Bhaskar A. Chemotherapy-induced peripheral neuropathic pain. BJA Education 2016; 16(4):114-119. https://doi.org/10.1093/bjaed/mkv044.
67. Staff NP, Grisold A, Grisold W and Windebank AJ. Chemotherapy-induced peripheral neuropathy: A current review. Ann Neurol 2017; 81(6): 772-761. https://doi.org/10.1002/ana.24951.
68. Zoodsma M, Sijmons RH, de Vries EGE and van der Zee AGJ. Familial cervical cancer: case reports, review and clinical implications. Hereditary Cancer in Clinical Practice 2004; 2(99). https://doi.org/10.1186/1897-4287-2-2-99.
69. Sijmons RH, Boonstra AE, Reefhuis J, Hordijk-Hos JM, de Walle HE, Oosterwijk JC, Cornel MC. Accuracy of family history of cancer: clinical genetic implications. Eur J Hum Genet 2000; 8(3): 181-186. https://doi.org/10.1038/sj.ejhg.5200441.
70. Hemminki K, Dong C, Vaittinen P. Familial risks in cervical cancer: is there a hereditary component? Int J Cancer 1999; 82(6): 775-781. https://doi.org/10.1002/(SICI)1097-0215(19990909)82:6<775::AID-IJC1>3.0.CO;2-V.
71. Magnusson PK, Lichtenstein P, Gyllensten UB. Heritabiliy of cervical tumours. Int J Cancer 2000; 88(5): 698-701. https://doi.org/10.1002/1097-0215(20001201)88:5<698::AID-IJC3>3.0.CO;2-J.
72. Andrews FJ, Linehan JJ, Melcher DH. Cervical carcinoma in both mother and daughter. Acta Cytol 1981; 25(1): 3-4. https://pubmed.ncbi.nlm.nih.gov/6937064.
73. Kiptoo S, Otieno G, Tonui P, Mwangi A, Orango O, Itsura P, Muthoka K, Oguda J, Rosen B, Loehrer P and Cu-Uvin S. Loss to follow-up in a cervical cancer screening and treatment program in western Kenya. JCO Glob Oncol 2018; 4(2): https://ascopubs.org/doi/10.1200/jgo.18.41300.
74. Stausberg J, Koch D, Ingeberf J and Betzler M. Comparing paper-based with electronic patient records: lessons learned during a study on diagnosis and procedure codes. J Am Med Inform Assoc 2003;10(5): 470-477. https://doi.org/10.1197/jamia.M1290.