

Histopathological patterns of cervical cancer among females presenting to a pathology core reference laboratory in Kampala, Uganda: A 5-year review

Abstract

Cervical cancer is the fourth most common cancer among women globally, with an estimated 604 000 new cases and 342,000 deaths in 2020, about 90% of these occur in low- and middle-income countries, having highest rates in sub-Saharan Africa. Cervical cancer is the leading cause of cancer morbidity and mortality in Ugandan women with estimated 6959 new cases and 4607 deaths in 2020. The histopathological differentiation of cervical cancer is a major determinant in treatment options and prognosis of disease. However, there is a paucity of data regarding this in Uganda. The study aimed to determine the histopathological pattern of cervical cancer among females presenting to Makerere university pathology core reference laboratory.

Methodology: A retrospective cross-sectional study employing the use of quantitative methods of data collection was conducted within Makerere university pathology core reference laboratory. The study obtained information on patients who had a cervical cancer diagnosis by histology from 2017 to 2021. The data was descriptively analyzed using SPSS version 21.

Results: A total of 120 patients from 2017 to 2021 were recruited into the study. The mean age of the patients was 47.5 (SD 13.1), the youngest patient was 21 and the oldest was 80 years. Cervical cancer was more prevalent in women aged between 35 to 54 years 77(64.2%) and women with HIV infection 26(21.7%). Squamous cell carcinoma present in 102 (85%) patients was the most prevalent pattern of cervical cancer. This was followed by adenocarcinoma 7(5.8%) and adenosquamous 5(4.2%) histological patterns of cervical cancer.

Conclusions: Cervical cancer is predominant among women with HIV and women aged 35-55 years. Squamous cell carcinoma is the most prevalent pattern of cervical cancer in Uganda present in every 9 out of 10 patients. Routine screening of all HIV positive women and women aged 35 and above is recommended.

Keywords: Histopathological Patterns, Cervical Cancer, Uganda

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Introduction

Cervical carcinoma is a malignant neoplasm that originates from the cervical epithelium, specifically the transformation zone of the cervix. The disease is characterized by a prolonged pre-invasive phase, during which the cervical epithelial cells undergo abnormal proliferation, known as Cervical Intraepithelial Neoplasia (CIN). These premalignant changes may either regress spontaneously or progress to invasive carcinoma if left untreated (Uganda_Cancer_Institute, 2017).

Persistent infection with Human Papillomavirus (HPV) infection is the primary etiological factor for cervical carcinoma. HPV is responsible for 99.7% of cervical cancer and infects 75%-80% of sexually active adults at some point, however, it can be cleared by the body's immune system most of the

Worldwide, cervical cancer is the fourth most frequent cancer in women with an estimated 604 000 new cases in 2020 (WHO, 2022a). Of the estimated 342,000 deaths from cervical cancer in 2020, about 90% of these occur in low- and middle-income countries. Women living with HIV are 6 times more likely to develop cervical cancer compared to women without HIV, and an estimated 5% of all cervical cancer cases are attributable to HIV [1-4].

In Uganda, the crude incidence rate of cervical cancer is estimated at 30 per 100 000, while the mortality rate was estimated at 19.9 per 100 000. Cervical cancer is the number one cause among women of both age-standardized cancer-related incidence and cancer-related deaths from all cancers in Uganda [5].

Like in other parts of the world, the involvement of Human Papilloma Virus (HPV) infection in this

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malignancy in Uganda is comparable to the rest of the world with HPV-16 and HPV-18 as the major oncogenic strains [6-8]. A 2011 review reported a number of estimates of high-risk HPV prevalence from 20 studies, ranging from 10.2% to 40% among HIV negative women and ranging from 37% to 100% among HIV positive women. The HPV prevalence estimates among women with normal cytology included in the HPV Information Centre report range from as low as 15.2% in women aged 25-60 to as high as 73.2% in women aged 12-24 (<https://prescriptec.org/>). Most of the prevalence studies were conducted prior to the introduction of the HPV vaccination programs in Uganda; therefore, these estimates may not reflect the current situation. The WHO recommends a screen-and-treat strategy to reduce incidence of cervical cancer (WHO, 2022a). The target age group is women 25 to 49 years old. Screening occurs every 3 years for HIV-negative women and annually for HIV-positive women. Midwives and nurses are the primary providers of cervical cancer screening as well as treatment (Nakisige et al., 2017). The screening methods include visual inspection with acetic acid (VIA), visual inspection with Lugol's iodine (VILI), colposcopy, and HPV testing and pap smear. Patients who screen positive should undergo histological confirmation for diagnosis of Cervical Intraepithelial Neoplasia (CIN) or cervical carcinoma (Uganda_Cancer_Institute, 2017).

Prior to enrollment of patients for cervical cancer treatment, a diagnostic or confirmatory test must be done to make a definitive diagnosis or confirmation of pre-cancer or cancer lesions (<https://prescriptec.org/>). Colposcopy, biopsy and Endocervical Curettage (ECC) are the most commonly used diagnostic tests for cervical cancer. Colposcopy and endocervical curettage are not routinely done in Uganda, and thus biopsy is the gold standard for the diagnosis of cervical cancer in Uganda. Biopsy is used to determine the degree of abnormality of the cell changes at the cervix and to rule out cancer. After examination, the result is classified as normal, as Cervical Intraepithelial Neoplasia (CIN), or as invasive carcinoma. The precancerous lesions are classified as low-grade (CIN1) or high-grade (CIN2 and CIN3, collectively referred to as CIN2+) pre-cancer. The World Health Organization (WHO) categorizes cervical intraepithelial neoplasia (CIN) according to the depth of the abnormal epithelial proliferation relative to the basement membrane. The proportion of cervical epithelium exhibiting dysplastic cells determines the grade of the dysplasia. Specifically, CIN is classified as low-grade (CIN1), if the abnormal epithelial proliferation extends less than one-third of the thickness of the epithelium; as high-grade (CIN2), if the abnormal epithelial proliferation extends for more than one-third but less than two-thirds of the thickness of the epithelium; and CIN3, if the abnormal epithelial proliferation extends for more than two-thirds of the thickness of the epithelium. Dysplasia becomes cancer when it invades the basement membrane.

For cancerous lesions, the histological pattern of the malignancy is also determined [9-12].

There are many histopathological patterns of cancer of the cervix. This must be determined as it influences treatment and prognosis of the disease. The common histopathological patterns are Squamous Cell Carcinoma (SCC), adenocarcinoma, adenoid cystic carcinoma, adeno-squamous carcinoma, clear cell carcinoma and mucinous carcinoma. Some of the tumors can be well differentiated, moderately differentiated or poorly differentiated tumors [13]. The aim of this study is to assess the histopathological patterns of cervical cancer in Uganda.

The commonest histological type of cervical cancer is squamous cell carcinoma (85%-90%) either well-differentiated or moderately or poorly differentiated. The sources of the squamous epithelium which turn into malignancy arise from squamo-columnar junction or squamous metaplasia of the columnar epithelium. Squamous cell carcinoma is further subdivided histologically into three groups: (i) large cell keratinizing, (ii) large cell non-keratinising and (iii) small cell type. Patients with small cell type have got poor prognosis compared to the large cell types. There's also a rare type; Basaloid Squamous Cell Carcinoma (BSCC) which is an aggressive variant of oral squamous cell carcinoma. Some patients present with adenocarcinomas, and others less commonly with mixed carcinomas (features of both squamous cell carcinoma and adenocarcinoma) of the cervix [14-16].

Other histopathological patterns of cervical cancer are adenocarcinoma (10%-15%) which develops from the endocervical canal, either from the lining epithelium or from the glands. Currently increased number of cervical adenocarcinomas are observed specially in the younger age group. The majority (80%) of them are purely endocervical type. The remainders are endometrioid, clear cell, adenosquamous or a mixed type. Adenoma-malignum is an extremely well-differentiated adenocarcinoma with favorable prognosis. Neuroendocrine tumors, sarcomas and lymphomas are rare tumors of the cervix [15, 17].

In a review conducted in Nigeria, poorly differentiated squamous cell carcinoma was the leading variants of cervical cancer. Squamous Cell Carcinoma (SCC) was seen in 90.8% patients while 7.1% patients had adenocarcinoma. One patient each had adenoid cystic carcinoma, adenosquamous carcinoma, clear cell carcinoma and mucinous carcinoma. In the same study, majority of the patients, (50.5%) had poorly differentiated tumors, 32.7% had well differentiated tumors, while the rest 16.8% had moderately differentiated tumors [16].

In another review conducted in India, the most common malignancy was squamous cell carcinoma (88.1 %) among which moderately differentiated squamous cell carcinoma comprised (73.1%) followed by well differentiated squamous cell carcinoma (11.3%) and poorly differentiated (3.7 %). Other variants of cervical cancer were papillary,

adenosquamous and basaloid variants (Priya and Indumati, 2020).

In a study done in Kenya in East Africa, the most prevalent histological type of cervical cancer was Squamous Cell Carcinoma (SCC) (89.9%), followed by Adenocarcinoma (AC) (5.6%). Two patients had anaplastic carcinoma, and another two had sarcoma of the cervix. Among those with SCC, most had moderately differentiated SCC (39.2%), with 32.0% and 21.3% having poorly differentiated and well differentiated disease respectively. At the time of diagnosis, the majority of patients (80.5%) presented with stage 2B disease or above [13].

Since histopathology is a cornerstone in the detection and the diagnosis of cervical cancer, studies have studied how histopathological classification of cervical cancer influence the management, treatment and surveillance planning of newly diagnosed cervical cancer. A study conducted in united states using the United States Surveillance, Epidemiology, and End Results (SEER) population data found out that Small cell carcinoma and adenocarcinomas were generally associated with poorer survival (Vinh-Hung et al., 2007). In the same study, cause-specific mortality hazard ratios by histological type relatively to non-micro-invasive squamous cell carcinoma were: micro invasive squamous cell carcinoma 0.28, carcinoma not otherwise specified 0.91, non-mucinous adenocarcinoma 1.06, adenosquamous carcinoma 1.35, mucinous adenocarcinoma 1.52 and small cell carcinoma 1.94. This study therefore greatly highlights the importance of histopathological classification of cervical cancer in determining treatment choices, morbidity and mortality due to the disease [14].

Despite known histopathological patterns of cervical cancer in different countries, the case is different for Uganda. There is a knowledge gap regarding histopathological patterns of cervical cancer among cervical cancer patients in Uganda. The purpose of this study was to address the gap.

Problem statements

The global burden of cervical cancer is heavily concentrated in low- and middle-income countries (LMICs), having the highest rates in sub-Saharan Africa (SSA) [8] In Uganda, due to an increased burden of HIV, the prevalence, morbidity and mortality from cervical cancer has been increasing in the recent years. Uganda ranks seventh in the world for cervical cancer incidence, with an estimated rate of 56.2 per 100 000 people in 2020 (compared to a global rate of 13.3) (Uganda_Fact_Sheet, 2020). Cervical cancer is the leading cause of cancer morbidity and mortality in Ugandan women with an estimated 6959 new cases and 4607 deaths in 2020 (Uganda_Fact_Sheet, 2020).

The histopathological differentiation of cervical cancer is a major determinant in treatment options

for cervical cancer and is a major determinant of prognosis of the disease. For example a study done in Romania demonstrated that cervical cancer patients with adenocarcinomas and adenosquamous carcinomas had a significantly poorer treatment response to chemo- radiotherapy than those with squamous cell carcinomas [7]. There is paucity of data regarding the histopathological cervical cancer patterns in Uganda. This makes it difficult to plan for appropriate treatment modalities aimed at maximizing treatment benefits for cervical cancer patients.

Justification

Histopathology and cytopathology form the scientific and clinical basis for current prevention and treatment of cervical cancer. Histopathology determines treatment of cancer and precancer through classifying into a diagnosis the patterns of microscopic organization of cells in tissue sections from biopsy or surgical specimens. Understanding the histopathological patterns of cervical cancer in Uganda will provide a basis for designing interventions to reduce cervical cancer morbidity and mortality. This will help reduce cancer related deaths and will lead to socioeconomic transformation.

Objectives- general objective

To determine the common histologic patterns of cervical cancer among females presenting to Makerere university pathology core reference laboratory.

Specific objective

To determine the factors associated with cervical cancer among females presenting to Makerere university pathology core reference laboratory.

Materials And Methods

Study design

This was a quantitative retrospective cross-sectional study. This study design helped the researcher collect enough information due for a period of 5 years in a short period of time.

Study area

The study was conducted within Makerere university pathology core reference laboratory found at Makerere University College of Health Sciences in Mulago hill, Kampala Uganda. The Makerere University pathology laboratory is a core reference laboratory in Uganda receiving different types of specimens from all over the country. Therefore, the information generated on cervical cancer patterns could be representative of the whole of Uganda.

Study population

The study population were cases of cervical cancer that had histology done from Makerere university pathology core reference laboratory from 2017 to 2021 as documented in the laboratory Health Management Information System (HMIS) books.

Selection criteria

This includes both inclusion and exclusion criteria.

Inclusion criteria

- i. Patients with a positive cervical cancer histology done from Makerere university pathology core reference laboratory.
- ii. Patient information must have been recorded in the HMIS books or in the computer
- iii. The histological diagnosis must have been made from 2017 to 2021

Exclusion criteria

Patient information incomplete such as unspecified type of cervical cancer. A total of 5 studies were excluded from the study due to missing information. This was mainly due to poor handwriting of the technician as the written information could not be read by the researcher during data collection.

Sample size determination

Total population sampling was used and therefore all reports belonging to patient's that met the inclusion /exclusion criteria were recruited in the study.

Sampling technique

Total population were be captured and processed for data analysis.

Data collection methods

The data collection guide was developed and then exported to a mobile data collection platform. For the purpose was therefore transferred from laboratory HMIS books to Epicollect 5.

Data analysis

The Data collected was analyzed using SPSS version 21.

Quality control

Pre-testing data collection tool was done before starting data collection to ensure that the tool is able to capture all necessary information. Only complete information was entered into the mobile data collection tool.

Ethical considerations

Ethical approval was obtained from the School of Biomedical Sciences Institution Review Board. Administrative clearance was obtained from Makerere university pathology core reference laboratory. Privacy and confidentiality of patient information was mentioned all the times by concealing patient identifiers and using strong passwords in computers containing patient data.

Results

Sociodemographic characteristics of respondents

In Table 1, a total of 120 patients from 2017 to 2021 were recruited into the study. The mean age of the patients was 47.5 (Standard deviation 13.1), the youngest patient was 21 years and the oldest was 80 years of age. Cervical cancer was more prevalent in women aged between 35 to 54 years 77(64.2%).

Associated conditions and stage at diagnosis

In table 2, majority of cervical cancer patients had associated HIV infection 26(21.7%). The stage of the cervical cancer at the time of diagnosis for majority of the patients 55 (45.8%) could not be determined. However, 24 (20.0%) patients had cervical cancer localized, 32 (26.7%) had a local spread and 3 (2.5%) patients had distant metastases.

Table 1: Sociodemographic characteristics of respondents.		
Variable	Frequency	Percentage
Age		
Less than 35	21	17.5
35 -44	34	28.3
45-54	33	27.5
55-64	21	17.5
65-80	11	9.2
Tribe		
Muganda	49	40.8
Munyankole	15	12.5
Musoga	9	7.5
Munyoro/Mutoro	6	5
Others	41	34.2

Table 2: Associated conditions and stage at diagnosis		
Variable	Frequency	Percentage
Associated condition		
HIV/AIDS	26	21.7
Pregnancy	4	3.3
Confirmed HPV infection	11	9.2
Family history of cervical cancer	3	2.5
None of the above	53	44.2
Stage at diagnosis		
Localized	24	20
Local spread	32	26.7
Regional spread	4	3.3
Distant metastases	3	2.5
Stage not determined	55	45.8

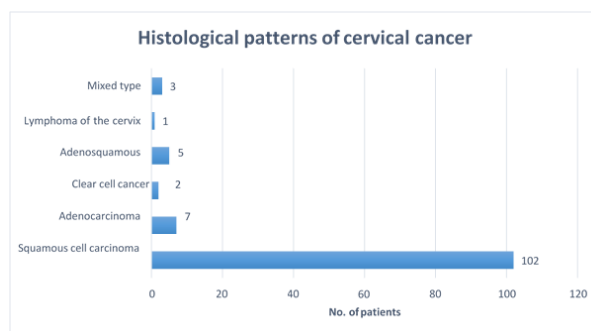


Figure 1: Histopathological patterns of cancer.

Histopathological patterns of cancer

Squamous cell carcinoma presents in 102 (85%) patients was the most prevalent pattern of cervical cancer. This was followed by adenocarcinoma 7 (5.8%) and adenosquamous 5 (4.2%) histological patterns of cervical cancer.

Discussion

This study showed that cervical cancer was more

prevalent in women aged between 35 to 54 years with an average age of diagnosis at 47.5 years. The findings are consistent with a 2022 report from United States of America which reported that cervical cancer is most frequently diagnosed in women between the ages of 35 and 44 with the average age at diagnosis being 50 [1]. The prevalence of cervical cancer increases with age due to long-lasting infection with certain types of Human Papillomavirus (HPV) among women, which later causes cervical cancer due to diminished immune functioning associated with increase in age.

The present study demonstrate that majority of cervical cancer patients had associated HIV infection. The findings are consistent with a report from WHO which showed that women living with HIV are 6 times more likely to develop cervical cancer compared to women without HIV (WHO, 2022b). In fact, HIV is responsible for around 5% of all cervical cancer cases worldwide and is the leading cause of death among women living with HIV [3]. Although the mechanism by which HIV increases risk of cervical cancer is not completely understood, studies suggest

that HIV-induced immunosuppression leads to an inability to control the expression of HPV and the production of HPV oncoproteins E6 and E7 [4-6]. According to Hawes and colleagues, this risk appears to be associated with increased HPV persistence that may result from immunosuppression related to HIV [7].

In the present study, squamous cell carcinoma patients was the most prevalent pattern of cervical cancer (85%). This was followed by adenocarcinoma 5.8% and adenosquamous 4.2% histological patterns of cervical cancer. The findings of this study correspond to findings of a study done by [5] which reported that was accounting for three-fourths of all cervical cancers. In the same study, adenocarcinoma and adenosquamous cell carcinoma represent 10–15%, and other or unspecified histology represent the remaining 10–15%. However, a study done by reported an overall increasing number of adenocarcinomas and adenosquamous carcinomas. A predominance of SCC in Uganda imply that treatment of cervical cancer with chemotherapy would increase the changes of response to treatment and decline in mortality. This is because SCC is associated with high chances of survival than other histological such as small cell carcinoma, several subtypes of adenocarcinoma-mucinous, clear cell, and common type of adenocarcinoma- and adenosquamous carcinoma [9].

Conclusions

Cervical cancer is more prevalent among women suffering from HIV and older women aged between 35 to 54 years.

Squamous cell carcinoma is the most prevalent pattern of cervical cancer in Uganda present in every 9 out of 10 cervical cancer patients.

Limitations

The accuracy of the information depended on the expertise of the pathologist who reported it. This raises a question of reliability of the findings. The study was a single-laboratory-based review and as such inadequate to draw conclusions, but it does shed some light on pathological pattern of cervical cancer in Uganda.

Poor handwriting by the technicians used to enter data in the HMIS.

Limited information provided by clinicians while referring patients to the laboratory

Recommendation

Routine screening of all HIV positive women and women aged 35 years and above is recommended.

Another study on this topic in Uganda is recommended

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