



Challenges faced in managing cervical cancer patients who present post-operatively with more advanced disease in LMICs: Case studies from Cameroon

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ABSTRACT

Cameroon is a low-and-middle income country (LMIC) with one of the highest incidence and mortality from cervical cancer in Africa. In this Central African country where the prevalence of human immunodeficiency virus (HIV) is high and the screening coverage is low, cervical cancer is the most deadly and the second most common cancer among women. Notwithstanding the growing burden of cervical cancer in Cameroon, most patients - often of lower socioeconomic status - continue to encounter multi-level barriers to timely and adequate care. These include the lack of physical and financial access to healthcare facilities, limited quality pathology, imaging and treatment services, ignorance of disease by the population, shortage of a well-trained oncology workforce, which result in significant delays in gaining access to screening, diagnosis, treatment and care. This paper presents 3 cases of patients with advanced cervical cancer who had surgery (hysterectomy) as primary treatment, without appropriate post-surgical investigation to further specify disease stage, persistence of residual disease, and need for adjuvant chemoradiation. Pathology services and diagnostic imaging procedures remain scarce and under-used in LMIC countries like Cameroon. Healthcare professionals involved in patient care lack adequate knowledge, skills and collaborative strategy to properly navigate these patients. To address these challenges, the health system should be reinforced with adequate infrastructures, sustainable funding should be secured to enhance universal health coverage and promote cancer prevention and control programs, multidisciplinary teams and coordination of care among providers should be improved, and relevant health indicators should be put in place to better monitor the quality of care delivered to patients who are mostly vulnerable and uninformed.

1. Introduction

Cameroon is a low-and-middle income country (LMIC) with an annual incidence of 2770 new cases of cervical cancer and a mortality of 1787 deaths in 2023, making it 13.4 % of all cancers diagnosed nationwide (ICO/IARC Information Centre on HPV and Cancer, 2023). Notwithstanding the growing burden of cervical cancer in this Central African country, most patients continue to encounter multi-level barriers to timely and adequate care across the country. These include the

lack of physical access to health facilities, limited quality pathology and imaging services, ignorance of the disease and financial constraints in gaining access to screening, diagnosis, treatment and care (Brand et al., 2019). Similar to most LMICs, disease presentation is mostly late (approximately two-thirds of cases are diagnosed at stage III and IV according to a population-based registry study conducted in 11 African countries) due to a delay in diagnosis which directly affects mortality rates (Sengayi-Muchengeti et al., 2020). Symptoms associated with this late presentation in LMICs include abnormal vaginal bleeding, pelvic

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pain, foul smelling discharge. In addition, lack of cervical cancer screening, older age at cancer diagnosis and being unmarried were found to be linked to advanced disease in LMICs (Nassali et al., 2018). Access to care is hampered by the significant economic burden cervical cancer imposes on individuals (Pearce et al., 2018). In this paper, we present 3 cases of patients with symptoms of cervical cancer indicative of advanced disease who were initially treated with surgery only with no post-surgical histological diagnosis and follow-up to refine clinical stage, margin status, and/or need for adjuvant chemoradiation.

2. Clinical cases description

2.1. Case 1

This is a case of a 37-year-old woman HIV Negative G3P3003 seen in our facility on 4/4/2021 with a recent history of persistent lower abdominal pain of two weeks duration. Pain was acute, radiating to the back with deep dyspareunia and post coital bleeding. In 2019, patient had a visual inspection with 5 % acetic acid (VIA) and 5 % Lugol's iodine (VILI) screening suspicious for cervical cancer (due to a large ulceroproliferative growth seen on the ectocervix with dense acetowhitening, multiple atypical blood vessels and contact bleeding) (Fig. 1). This prompted the attending clinician to do an ectocervical punch biopsy; and the pathology report showed invasive squamous cell carcinoma invading greater than 2 mm of cervical stroma and lympho-vascular space involvement. A pelvic scan of this patient showed a hypoechoic cervical mass of 1.4×1.0 cm and a tiny posterior wall myoma. After a long wait time owing to the shortage of gynecologic and surgical oncologists in Cameroon, this patient was evaluated by a medical oncologist in early 2020, then referred for surgical intervention after staging as 1B2 according to the International Federation of Gynecology and Obstetrics (FIGO) classification of cervical cancer, for which a radical hysterectomy was recommended. The surgery was performed in May 2020 with no major immediate or short-term complication; however, the hysterectomy specimen was not sent to the lab for pathology assessment. In April 2021, this patient visited our health facility with a complaint of left leg swelling for which a left leg ultrasound showed partial deep venous thrombosis (DVT) of the femoral vein, hence placed on warfarin tablets. She was given a follow up appointment for further evaluation but did not show up at our facility until the following year, reportedly because of the long distance between the hospital and her place of residence, and the lack of financial resources. In the month of January 2022, patient consulted the hospital again since she had persistent symptoms of swollen left leg and lower abdominal pain for more than 10 months. Pelvic Ultrasound revealed bilateral ovarian cystic masses right ovary (7×6.8 cm) and left ovary (9.1×8.5 cm).

Other associated symptoms included frequent urinating and weight loss, and patient was referred for oncology consultation. The physician went further to order a Pelvic CT scan which showed left hydronephrosis, large pelvic lobulated solid cystic mass extending more on the left pelvic sidewall with infiltration of the iliopsoas muscle and probable bladder infiltration. Neither the pelvic ultrasound nor pelvic CT scan commented on the presence or absence of the uterus. The patient was then referred for palliative chemotherapy for symptom control and is currently responding to treatment.

2.2. Case 2

A 48 yr HIV negative patient presented on 28th November 2021 in our facility with heavy vaginal bleeding for one day, associated with lower abdominal pain radiating to the back. She was treated medically and discharged after these symptoms had subsided. She returned to the hospital on the 3rd of December 2021 with similar symptoms of heavy vaginal bleeding and associated lower abdominal pain radiating to the back. Gynecological examination showed a suspicious cervical lesion based on a proliferative growth visible on the anterior lip of the cervix with acetowhitening and bleeding at VIA/VILI examination (Fig. 2) for which a punch biopsy was done. The punch biopsy revealed a high-grade cervical intra-epithelial neoplasia (HSIL, CIN2) with no histological sign of invasion, hence prompting thermal ablation as recommended intervention by the World Health Organization (World Health Organization, 2021). About two months later, this patient suffered similar symptoms for which a thoraco-abdomino-pelvic scan was done showing a hyper-vascularized endometrial mass with cystic portions within and homogenous splenomegaly. She was then referred to a reference hospital for better management. Advised by a family member, she ended up in a private clinic where a total abdominal hysterectomy (TAH) was done. We did not have access to the post-operative report to know more about the surgery. She was only seen in a hospital on the 14th of June 2022 presenting with chest, back and abdominal pain. Chest X-ray revealed lesions in the lungs and spine X-ray revealed osteolytic lesions (Figs. 3a and 3b). According to her records, no post-surgical histopathological analysis was performed after this TAH procedure at the said private clinic. This prompted a second referral to the reference hospital for proper evaluation and management. In this hospital, a thoraco-abdomino-pelvic CT scan was done reporting: a subtle L5 lytic lesion and numerous bilateral lung nodules up to 1.9 cm concerning for metastasis and a large spleen. At this late stage of disease, this patient is currently receiving palliative care with very little improvement in symptoms.

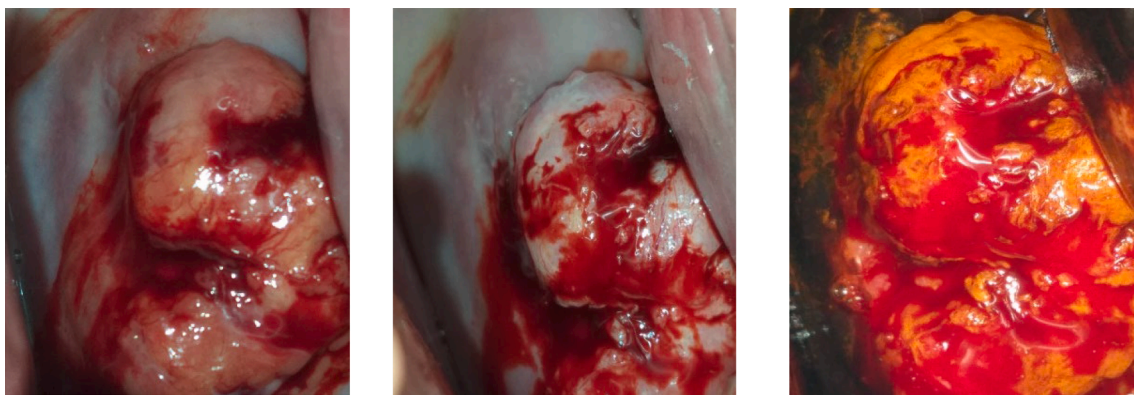


Fig. 1. (Date: 06/11/2019): 1a: Cervix without staining 1b: VIA (Visual Inspection of the cervix after application of 5% Acetic Acid) 1c: VILI (Visual Inspection of the cervix after application of 5% Lugol's Iodine). Cervigrams taken before, after the application of 5 % acetic and 5 % Lugol's Iodine respectively, showing a large ulceroproliferative growth on the cervical mucosa with dense acetowhitening and bleeding, for which invasive squamous cell carcinoma was diagnosed from pathology.

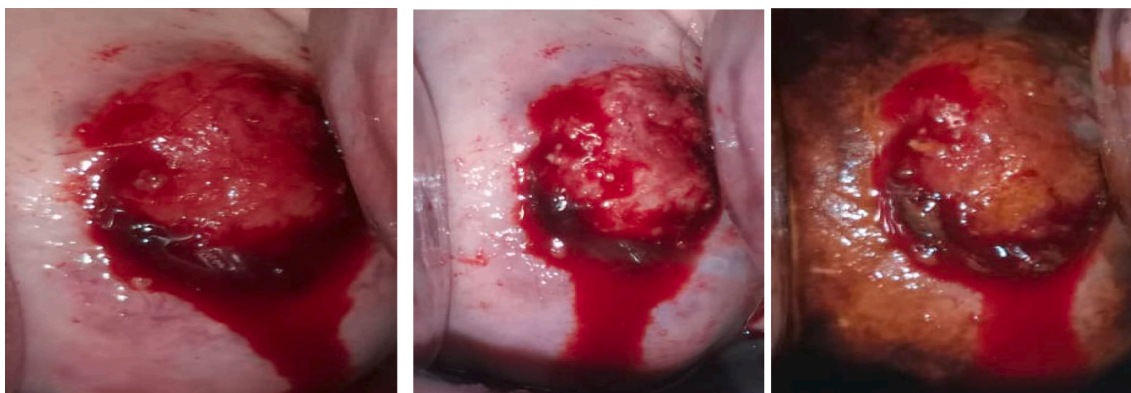


Fig. 2. (Date: 13/03/2021): 2a: Cervix without staining 2b: VIA (Visual Inspection of the cervix after application of 5% Acetic Acid) 2c: VILI (Visual Inspection of the cervix after application of 5% Lugol's Iodine). Cervigrams taken before, after the application of 5% acetic and 5% Lugol's Iodine respectively, showing a proliferative growth on the anterior lip of the cervix with acetowhitening and bleeding, for which a high-grade cervical intra-epithelial neoplasia (HSIL, CIN2) was diagnosed from pathology.

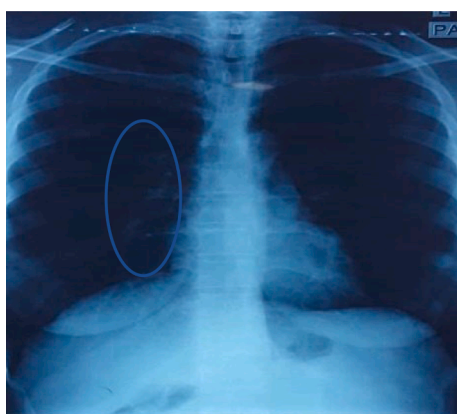


Fig. 3a. Chest X-Ray showing lesions in the lungs.



Fig. 4. Cervigram taken in December 2019 (cervix without staining) during the first patient consultation. Cervix fungating with an aggressive 3–4 cm mass and abnormal blood vessels, for which an invasive squamous cell carcinoma was diagnosed from pathology.



Fig. 3b. (Spine X-Ray) showing L5 lesion.

2.3. Case 3

This is the case of 37-year-old HIV positive woman who was first seen in December 2019 with a more than 6 months history of postcoital bleeding. She lives in a remote and rural area and did not have enough financial resources to travel and consult in a referral hospital, which led to delays in this patient's management. Evaluation of the cervix revealed a 3–4 cm fungating cervical mass (Fig. 4) involving the left parametrium. An ectocervical punch biopsy was done revealing invasive squamous cell carcinoma tumor invading greater than 2 mm of cervical

stroma with lympho-vascular space involvement. This case was categorized as stage 2B by the consultant and then referred for chemotherapy. She did not go for this treatment but instead ended up in a private clinic in January 2020 where a TAH was done, with no pathology report seen in her records. A few months later, she began having left leg pain prompting consultation in May 2021. Among investigations done, left deep vein thrombosis (DVT) was found and she was placed on Warfarin tablets. By January 2022, this woman started having anal and vaginal pain prompting another consultation. This time, a pelvic scan was done showing hydronephrosis of kidneys with bilateral ovarian masses, right 7 X 6.8 cm and left 9.1 X 8.5 cm. A CT scan was ordered which showed lobulated atypical mass involving left sidewall, ileo-psoas muscle and infiltrating the urinary bladder. From then hence forth, this case has been managed for recurrent cervical cancer with palliative chemotherapy involving paclitaxel/cisplatin combination with minimal improvement in symptoms.

3. Discussion

The above cases have in common: symptoms, inadequate diagnostic work ups, poor patient navigation, lack of post-surgical histopathological analysis and their relatively young ages. These cases are not uncommon in clinical practice, and they reflect a number of challenges faced by doctors in managing cervical cancer patients in LMICs like Cameroon, including: (i) at the health system level, the lack of health infrastructures adequately equipped with diagnostic services

(pathology, imaging procedures such as CT scan and MRI); the limited number of cancer treatment facilities (radiation therapy, chemotherapy, and palliative care services); and a limited access to a universal health coverage (UHC) system that does not cover cancer cases; (ii) at the provider level, the lack of physicians adequately trained to treat cancer patients, the limited number of specialist doctors in rural areas, and the lack of communication and coordination between physicians involved in cancer care (for example, through multidisciplinary tumor boards); and (iii) at the patient level, the limited understanding by patients of their condition, the stigma associated with the diagnosis of cancer, and the lack of financial resources that may result in delays in accessing healthcare facilities and in receiving care, misdiagnosis and potentially inappropriate or insufficiently informed decisions about their care.

The first case presented with symptoms such as dyspareunia, post coital bleeding and severe lower abdominal pain. In LMICs like Cameroon, 68 % of cervical cancer cases present with symptoms which are generally indicative of advanced disease (Annede et al., 2019). MRI and/or CT scan which are gold standard techniques for the staging of cervical cancer cases, are limited to major cities and the costs are prohibitive for the majority of patients and their family. Because surgery is not indicated for the treatment of advanced cervical cancer cases due to disease extension to various organs/tissues, chemoradiation remains the standard of care for locally advanced cervical cancers. In such cases, surgery followed by chemoradiation is not the current standard. In the absence of an adequate coordination and communication mechanism between physicians involved in patients' care, and considering the lack of a well-structured referral and counter-referral system, the lack of chemotherapy services and well-equipped radiation centers in many LMICs, some patients may be treated surgically solely, which may result in residual disease and surgery-related complications, leading to poorer outcomes. (Wilson et al., 2018) Post-surgical histopathology and imaging procedures were not performed in this case, which could have contributed to providing appropriate post-surgical care by refining the disease stage. Generally, diagnostic facilities including pathology services and limited in Cameroon. This case was probably at a more advanced stage than stipulated but due to lack of post-surgical histopathology evaluation, correct stage could not be ascertained.

The second case also presented with symptoms though the histopathology report of the ectocervical biopsy showed a high-grade cervical intra-epithelial neoplasia (HSIL/CIN2) which can be managed by ablative therapy in the absence of invasive disease, per WHO's guidelines. Probably an endocervical curettage (ECC), an endometrial biopsy or a loop electrosurgical excision procedure (LEEP) could have revealed more than just an HSIL/CIN2 in this patient. This further portrays risk of missing out lesions on cervix with partially visible transformation zone (type 3 TZ) during screening with visual methods (Manga et al., 2021). In addition to estrogen cream, Misoprostol is currently being investigated as a potential remedy to convert type 3 TZ to type 1 or 2 during cervical cancer screening based on VIA/VILI (Manga et al., 2022). In 2–12 % of patients with type 3 TZ lesions, atrophy analysis and ectocervical biopsies as in this case, would not detect any lesion in the cervical canal (Wei et al., 2023). These occult lesions that are missed out, can progress rapidly to more advanced disease. Still as a result of underused pathology services in Cameroon, a TAH was done about two months later when a hyper-vascularized endometrial mass was seen on her pelvic scan report. No surgical specimen was sent for histopathological analysis to ascertain tumor type and disease stage. This highlights poor navigation of care for patients presenting with suspected malignancy in limited-resources settings.

The third case presented with symptoms indicative of advanced disease confirmed by staging. This patient was HIV positive, and HIV infection is known to increase the risk of cervical cancer by 6 folds (Stelzle et al., 2021). HIV prevalence in the adult population in Cameroon is estimated at 3.7 % and is about two times higher among women (5.0 %) than men (2.3 %) (The Cameroon Population-based HIV Impact assessment, 2018). While treatment of cervical cancer is the

same in HIV positive women as in HIV negative women, most clinicians in Cameroon treat cervical cancer in HIV positive women when they have achieved viral suppression (undetectable viral load) and/or improved immune response (CD4 count above 200cells/ml) to reduce treatment-related complications and risk of disease recurrence. Since most HIV positive women in LMICs like Cameroon are on antiretroviral therapy, HIV may delay the treatment of cervical cancer by a few weeks or months, and/or cause more serious complications in some HIV positive women. Despite being referred for chemoradiation, this patient ended up in a clinic where a TAH was done. Currently, Cameroon lacks adequate radiotherapy units with only two found in Douala, a big town with relatively high cost of living. Among these two functioning radiation centers, the older one (opened in 1991 and equipped with conventional radiation techniques using gamma radiation from a Cobalt-60 source, and rehabilitated in 2021 with the technical assistance of the International Atomic Energy Agency (IAEA)) is owned by the government (treatment partly subsidized, average cost of 511,000 CFA francs (about \$850) per treatment plan) while the most recent one (opened in 2019 and equipped with modern radiation techniques, including a medical linear accelerator and a computerized treatment planning system) is a private owned radiotherapy center (not subsidized by the government) that charges 2,000,000 CFA francs (about \$3,330) per treatment plan. This patient may have preferred the surgical option apparently cheaper (average cost of 350,000 CFA francs, which is about \$580) compared to chemoradiation with a promise of cure from the specialist who carried out the intervention, and considering the long wait times (up to 3 to 6 months) between the inclusion of patients on the radiotherapy list and the actual start of treatment for those who cannot afford treatment in the private radiotherapy center. This case further reflects the huge economic burden for most patients diagnosed with cervical cancer in LMICs, including Cameroon.

Multiple barriers limiting access to radiotherapy services have been identified in LMICs. In Cameroon, the most important barriers remain the small number (only two radiation units are currently operational), the uneven distribution (both units located in the economic capital of the country) and the high cost of these services. While a UHC system has been recently introduced into the public health sector in Cameroon, community enrollment remains suboptimal and only a few health conditions (primarily, infectious diseases, and maternal and child health conditions) are covered under this program. To date, cancer care including radiotherapy is not included into this UHC benefits 'package'. As a result, most cervical cancer patients have to pay for radiation services on their own, and the relatively low government subsidy for radiotherapy makes this critical treatment out of reach to most patients in Cameroon, especially low-income patients and those residing in rural areas. This leads to delays in access to care, and poorer treatment outcomes. Other barriers to timely access to radiation in Cameroon include patient factors (age, comorbidities, lower awareness), physician factors (referral bias, physician preferences), and geographical factors (distance of facility from residence) (Maitre et al., 2022). Therefore, it is essential to invest in establishing and expanding modern radiation units and cancer centers in Cameroon and other LMICs. These centers should be equipped with adequate diagnostic tools, treatment facilities, and a multidisciplinary team of healthcare professionals specialized in oncology.

Overall, the 3 clinical cases presented in this article have several peculiarities that underpin the challenges faced by cervical cancer patients in Cameroon. These include the lack of oncology training for healthcare providers in the country. Specialized medical training in Cameroon is available in a few medical schools for pathologists, radiologists, general surgeons, gynecologists. Although some surgeons and gynecologists operate cancer patients, there persists among most doctors a lack of standard-of-care skills and competencies to perform complex surgical procedures like radical hysterectomy. While residency training for medical oncologists and radiation oncologists was recently introduced, there is no sub-specialized training for gynecologic or surgical

oncologists in Cameroon. To enhance the skills of doctors involved in oncology care in this Central African country as in most LMICs, training curricula should be updated to include more hands-on experiences and continuing medical education focused on cancer prevention and care, and health infrastructures where these doctors are trained should be properly equipped. (Fokom Domgue et al., 2023 Jan). On the other hand, the collaboration between providers should be reinforced for a better coordination of care. A potentially low-cost digital health and telementoring platform for the continuing education of the healthcare workforce has proven effective at improving clinical competencies, collaboration, and coordination of care among healthcare providers involved in women's cancer prevention and treatment in Cameroon and other African countries (Fokom Domgue et al., 2023 Jan; Fokom Domgue et al., 2022), and could serve as a practical way to expand and promote the development of virtual tumor boards in LMICs. Further, providers should acknowledge their levels of competencies and when not adequately skilled at performing certain procedures, they should consider collaborating with more experienced colleagues or even referring patients with complex cases in centers where proper treatment will be provided to the patient.

Despite ongoing efforts of the government to improve the Cameroonian health system, there are limited cancer centers in Cameroon to meet the heavy demand of cancer patients. A few cancer centers available in Cameroon are found in urban areas; while many cervical cancer patients reside in rural settings and would not meet the financial requirements to be treated in these centers. The national programs for the control of HIV/AIDS, malaria and tuberculosis have benefited from substantial financial support from the Global Fund and technical assistance from WHO, UNICEF and other partners, which have resulted in improvements in care and patient outcomes. Lessons learned from these programs should be applied to the control of cervical cancer in Cameroon, and integration of cancer care into existing HIV care programs should be considered to achieve greater impact.

Another challenge encountered is the lack of public awareness and knowledge about cervical cancer. Although there is no national plan to raise population awareness about this cancer, health education is often done at different levels, including healthcare facilities, communities, newspapers, radio, TV, however, coverage remains low. Many healthcare providers are not knowledgeable about the disease, including how to perform cervical cancer education and counselling (Fokom Domgue et al., 2023 Jan). Most patients have a low level of health literacy, considering that many of them reside in remote settings where they are poorly exposed to screening services and accurate information. Even with accurate information, some are deceived to go for surgery because it is a cheaper option not minding the stage and post-surgical morbidity. Non governmental organizations (NGOs) and civil society organizations (CSOs) involved in the health sector in Cameroon should be empowered and incentivized to contribute more actively to the community education about cervical cancer. In fact, creating awareness on cervical cancer screening and HPV vaccination are cost-effective ways to preventing the disease in the population, as these interventions have proven to be feasible and effective in Cameroon (Fokom Domgue et al., 2020 Jul 1; Tebeu et al., 2015). In addition, many studies have reported that knowledge about HPV vaccination and cervical cancer screening remains poor in most African countries, including Cameroon (Okoyere et al., 2021 Jun 5; Fokom Domgue et al., 2024 Jan; Elit et al., 2022). Importantly, Cameroon needs to empower patients diagnosed with cancer through a health insurance scheme that can cover a proportion of their bills. This will go a long way to reduce mortality which currently stands at about 13,200 annual deaths in Cameroon (ICO/IARC Information Centre on HPV and Cancer, 2023).

To improve cancer patients' outcomes in LMICs, it is essential to put in place culturally relevant solutions that strengthen technological progress, promote mutually beneficial partnerships, and adopt tailored interventions. Access to timely cancer care relies on strong health infrastructures and operational health systems. Enhancing health

infrastructure and optimising resources allocation constitute the backbone of quality cancer care delivery in LMICs. In this regard, collaboration between governmental and non-governmental organizations is critical to ensure lasting funding for cancer care, drug access programs, and healthcare workforce's capacity building. Such collaborations would facilitate knowledge and skills transfer, allowing professionals to acquire skills and competencies in specialized cancer care and health management, thereby improving access of vulnerable populations to standard-of-care services. In addition, innovative technologies that can bridge the gap between patients and providers, such as telemedicine and mobile health applications, may contribute to optimizing cancer care in LMICs like Cameroon. These technologies have the potential to strengthen providers' efficacy, improve patients' outcomes, and reduce healthcare expenditures in LMICs (Kabukye et al., 2021, Ahmed et al., in press). To that end, the use of machine learning and artificial intelligence (AI) methods, which may help address some capacities problems encountered by healthcare systems in limited-resource settings by assisting healthcare providers in making timely decisions about patients care, can contribute to improving access to care and to fostering equitable allocation of scarce health resources in LMICs (Stefan and Tang, 2023).

4. Conclusion

To improve quality of cervical cancer care, accurate diagnosis and proper disease classification (tumor type and stage) are necessary through pathology and imaging procedures, and well-equipped treatment facilities with functioning chemoradiation services and a multidisciplinary oncology workforce should be made available to most patients. Such services remain scarce and underused in LMIC countries like Cameroon. Health professionals often lack the appropriate knowledge, skills and collaborative strategy to properly navigate these patients, and patients are not adequately educated about cervical cancer and lack financial resources to timely access these services. To address these challenges, health system should be reinforced with adequate infrastructures, sustainable funding should be secured to enhance universal health coverage and promote cancer prevention and control programs, mutidisciplinary teams and coordination of care among providers should be improved, and relevant health indicators such as disease staging and the proportion of disease recurrence should be put in place to better monitor the quality of care delivered to patients who are mostly vulnerable and underinformed.

Informed consent statement

Written consent was obtained from patients for publication of this case series and accompanying images.

Final approval: All authors.

CRedit authorship contribution statement

Calvin Ngalla: Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Conceptualization. **Jaff Didymus:** Writing – review & editing, Methodology, Data curation. **Florence Manjuh:** Writing – review & editing, Project administration, Methodology, Data curation. **Marius Nwufor:** Writing – review & editing, Data curation. **Joseph Nkfusai:** Writing – review & editing, Methodology. **Laure Elit:** Writing – review & editing, Supervision, Methodology. **Joel Fokom Domgue:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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