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Feasibility of neoadjuvant chemotherapy for bulky early stage to stage IIIB cervical cancer in Uganda

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ABSTRACT

Introduction: External beam radiotherapy (EBRT) became unavailable in Uganda from February 2016 to November 2017. Following resource stratification guidelines, an alternative treatment strategy was developed.
Methods: Bulky early stage to Stage IIIB patients received at least 3 cycles of neoadjuvant chemotherapy (NAC). Surgery was performed if adequate response was achieved and adjuvant therapy given for high risk factors. Chemotherapy versus supportive care was advised in unresectable disease. NAC protocol completion was defined as receiving at least 3 cycles of NAC followed by either surgery, chemotherapy and/or radiation, or best supportive care. The purpose of this study was to determine the completion rate of NAC and assess the adverse events associated with treatment. Data were collected through retrospective chart review.
Results: From February 2016 to November 2018, 53 evaluable patients were identified. 86.8% (46/53) of patients presented in Stage IIB or higher. The completion rate of the NAC protocol was 75.5% (40/53). 94.3% (50/53) received platinum-taxane combination. 7.6% (4/52) grade 3 adverse events occurred related to chemotherapy, all hematologic. 18.8% (10/53) patients underwent surgery with 2 aborted cases due to metastatic or inoperable disease. No adverse events related to surgery were reported. 5 patients underwent adjuvant therapy after surgery due to high risk factors or incomplete pathology findings. 26 patients received adjuvant radiation (3 brachytherapy, 23 EBRT after it became available). Reported side effects related to radiation included vaginal fibrosis and skin reactions.
Conclusion: In this limited-resource setting, majority of patients completed a NAC treatment strategy for cervical cancer with acceptable toxicities.

1. Introduction

Globally, cervical cancer has the fourth highest incidence and mortality, with an estimated 660,000 new cases and 350,000 deaths in 2022 (Bray et al., 2024). Notably, cancer incidence to mortality ratio is disproportionately higher in low and middle income countries. East Africa has a 40.4 % incidence of cervical cancer with a mortality rate of 28.9 % compared to North America with an incidence of 6.3 % and mortality of 2.2 % (Bray et al., 2024). Cervical cancer is the leading cause of cancer-related deaths in Ugandan women. In 2021, WHO estimated that approximately 6,738 Ugandan women are diagnosed with cervical cancer every year, with 4,400 dying from the disease (WHO, 2021).

The disproportionate burden of cervical cancer deaths in low and middle income countries are due to challenges in access to care, effective screening and prevention programs (Bruni et al., 2022), and limited available cancer therapies. In 1999, the standard of care treatment for bulky early stage and locally advanced stage disease became chemoradiation worldwide (Morris et al., 1999; Rose et al., 1999; Whitney et al., 1999; Keys et al., 1999); however, access to radiotherapy and adherence to guideline recommended treatment remain key barriers to effective treatment (Mayadev et al., 2022). Interest in neoadjuvant

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chemotherapy (NAC) for cervical cancer arose from the desire to decrease need for adjuvant radiation (Rydzewska et al., 2012; Katsumata et al., 2013), decrease surgical morbidity (Eddy et al., 2007), and improve survival in advanced stages (Kokka et al., 2022). NAC may be an alternative strategy in resource-limited settings.

NAC is included in the National Comprehensive Cancer Network (NCCN) resource stratification treatment guidelines based on available resources to treat cervical cancer (NCCN, 2024). First published in March 2015, this resource stratified framework emphasizes utilizing the best available resources and if basic resources are unavailable, palliative and best supportive care should be given. There are limited published experiences of real-life feasibility of translating these framework guidelines into clinical practice.

Mulago National Specialised Hospital and the Uganda Cancer Institute (UCI) are the main hospitals that provide cancer care for patients in Uganda. In February 2016, the sole cobalt-60 teletherapy unit for the country ceased functioning. Without external beam radiotherapy, curative treatment for cervical cancer patients was no longer available. Provisional care was arranged with the Ministry of Health of Kenya to allow patients to receive radiotherapy treatment in Kenya until a new radiotherapy unit could be established in Uganda. However, most patients could not receive care in Kenya due to logistical hurdles and limited availability. Chemotherapy agents for cervical cancer were available in Uganda. Although the timeline was unclear, the Ugandan government was actively procuring replacement for external beam radiotherapy. Chemotherapy was an intervention under investigation. We needed to study its impact under the prevailing circumstances. NAC was offered during this period when external beam radiotherapy was temporarily not available in Uganda to patients who would have otherwise benefitted from definitive chemoradiation. Best supportive care was an option for patients with poor performance status or with metastatic advanced or recurrent disease. The purpose of this study was to determine the completion rate of NAC for cervical cancer patients and assess the adverse events associated with treatment modalities.

2. Methods

A multidisciplinary taskforce was formed to develop an alternative treatment approach for patients who were unable to receive definitive chemoradiation treatment in Kenya. Members of the taskforce included UCI medical oncologist, UCI radiation oncologist, experienced gynecologists caring for patients with gynecologic malignancies from UCI and Mulago Hospital, one fellowship trained gynecologic oncologist at Mulago Hospital, and board-certified gynecologic oncologist mentors from different academic institutions in the United States. Chemotherapy and high dose rate (HDR) brachytherapy were administered at UCI. Surgery was performed by local faculty and an international gynecologic oncologist mentor. During the study period, a formal gynecologic oncology training program was in process at UCI, with international mentors supporting the surgical and clinical expertise of local faculty.

As the study was conducted at the Uganda Cancer Institute and supported by Duke Hospital investigators, IRB approval was required and obtained at both sites. Eligibility criteria included untreated bulky (>4 cm) early stage to Stage IIIB (2009 FIGO staging) biopsy proven cervical cancer of all histologic types. Clinical staging was determined based on exam, ultrasound, and chest x-ray given available resources. Subjects had no access to external beam radiation and were deemed eligible to receive platinum-based chemotherapy. Exclusion criteria were Stage IVA-IVB cervical cancer and ECOG performance status >2. Bulky (>4 cm tumor size) stage IB2-IIA patients could be offered immediate radical hysterectomy.

All eligible patients were prescribed standard platinum-based combination chemotherapy based on clinical characteristics and drug availability at UCI. The NAC protocol included at least 3 cycles of NAC followed by radical hysterectomy if response was present by pelvic exam and patient was an appropriate candidate for surgery. Adjuvant therapy after radical hysterectomy was recommended if high risk factors were present on final pathology including positive surgical margins and lymph node metastasis (Benedetti-Panici et al., 2002). In the absence of pelvic RT, additional chemotherapy and/or HDR brachytherapy (when surgical margins were positive) were recommended. In patients who were not surgical candidates, additional chemotherapy could be given if tumor response was present. If disease progression occurred, alternate chemotherapy versus discontinuation of treatment and hospice care was advised. Palliative HDR brachytherapy was offered to alleviate symptomatic bleeding that was refractory to chemotherapy. Completion of this NAC protocol was defined as receiving at least 3 cycles of NAC followed by either surgery, additional chemotherapy and/or radiation, or best supportive care. When external beam radiation therapy became available, patients receiving NAC were referred to definitive radiation therapy.

Study data were collected retrospectively through medical chart review and managed using the REDcap (Research Electronic Data Capture) electronic data capture tools hosted by Duke University. REDcap is a secure, web-based application designed to support data capture for research studies (Harris et al., 2009). Descriptive statistical analyses were performed using IBM SPSS statistics (version 28).

3. Results

From February 2016 to November 2018, 57 eligible patients treated at UCI were identified. 4 patients were excluded due to incomplete records, leaving 53 evaluable patients. External beam radiation therapy became available at UCI in December 2017 and no patients were offered NAC after this time point. Demographic data are presented in Table 1. Of the 14 patients with a diagnosis of HIV, all were receiving antiretroviral therapy. Only 11 patients reported having prior cervical cancer screening with visual inspection with acetic acid (VIA). All patients received baseline imaging, with ultrasound as the most common modality. 86.8 % (46/53) of patients presented in Stage IIB or higher. Only 7 patients presented with bulky early stage disease. There were no cases of immediate hysterectomy for bulky stage IB2-IIA patients (FIGO 2009

Table 1
Patient and disease characteristics.

Characteristic	N = 53
Age	50 [25–75]
Baseline ECOG PS	
0	6 (11.3%)
1	46 (86.8%)
2	1 (1.9%)
BMI	23 [16–34]
HIV	
Positive	14 (26.4%)
Negative	33 (62.3%)
Unknown	6 (11.3%)
Diabetes	1 (1.9%)
Hypertension	12 (22.6%)
Renal Insufficiency	2 (3.8%)
Prior cervical cancer screening	11 (20.7%)
Tumor size on exam	6 cm ±1.8
Baseline Imaging	
Abdominal ultrasound	53
Pelvic ultrasound	49
Chest X-ray	49
CT abdomen/pelvis	1
2009 FIGO Stage	
IB2	4 (7.5%)
IIA	3 (5.7%)
IIB	27 (50.9%)
IIIA	4 (7.5%)
IIIB	15 (28.3%)
Histology	
Squamous cell carcinoma	46 (86.8%)
Adenocarcinoma	3 (5.7%)
Other	4 (7.5%)

staging).

The completion rate of the NAC protocol was 75.5 % (40/53). After at least 3 cycles of NAC, 18.9 % (10/53) patients proceeded to surgery, 47.2 % (25/53) patients received additional chemotherapy and/or radiation, and 9.4 % (5/53) patients received best supportive care. Of the 13 of patients who did not complete the NAC protocol, 3 patients were lost to follow up after receiving 3 cycles of NAC and 10 patients did not complete a minimum of 3 cycles of NAC, with the most common reason due to lost to follow up.

Table 2 describes treatment modalities received on the NAC protocol. 94.3 % (50/53) patients received platinum and taxane combination neoadjuvant chemotherapy. 2 patients could not proceed due to costs of care and 1 was lost to follow up after initial consultation. Cisplatin 50 mg/m^2 and Paclitaxel 135 mg/m^2 every 3 weeks were the most common regimen. The median number of NAC cycles for the entire cohort was 4 (Bray et al., 2024; WHO, 2021; Bruni et al., 2022; Morris et al., 1999; Rose et al., 1999; Whitney et al., 1999). 7.6 % (4/52) grade 3 adverse events related to chemotherapy occurred, all hematologic.

18.8 % (10/53) patients underwent surgery with intent to perform hysterectomy, with 2 aborted cases. One was found to have a grossly positive obturator lymph node that was removed and the other case was aborted after exam under anesthesia revealed larger extent of disease. The average length of time from last cycle of NAC to surgery was 37.1 days ±19.1. The most common reason for not pursuing surgery was disease progression or inoperable disease. No adverse events related to surgery were reported. Of the 5 patients who received adjuvant therapy after surgery due to high risk factors on final pathology or incomplete pathology reporting, 4 patients underwent additional chemotherapy and 1 patient underwent both chemotherapy and brachytherapy.

26 patients ultimately received adjuvant radiation therapy. Prior to external beam RT availability, 3 patients received brachytherapy only while the remaining 23 patients received external beam therapy after it became available in December 2017. Reported side effects related to radiation included 1 case of vaginal fibrosis and 4 cases of skin reactions (severity of reactions were not documented). There was one death during the study period that was due to disease progression.

Table 2
Treatment received on NAC protocol.

Treatment	N
Chemotherapy regimen	
Cisplatin/Paclitaxel	45 (90%)
Carboplatin/Paclitaxel	4 (8%)
Cisplatin/Docetaxel	1 (2%)
Surgery	10 (18.8%)
Radical hysterectomy	7
Simple hysterectomy	1
Aborted hysterectomy	2
Final pathology	
Residual disease	
Yes	8
No	0
Not applicable	2
Lymph node metastasis	
Positive	2
Negative	4
Not reported/incomplete	3
Not applicable	1
Margin status	
Positive	0
Negative	5
Not reported/incomplete	3
Not applicable	2
Adjuvant Radiation	26 (49%)
HDR Brachytherapy only	3
External Beam only	6
HDR + External Beam	17

4. Conclusion

In this retrospective cohort study, our results show a 75.5 % completion rate of a NAC protocol when external beam radiotherapy was temporarily not available in Uganda. Lost to follow up was the most common factor to noncompliance to the protocol. An overall low rate of toxicities was reported with treatment modalities. Our study adds to the limited published experiences of real-life implementation of available cancer-directed therapies in a resource constrained setting (Chuang et al., 2016; Musa et al., 2016; Wijeratne and Hapuachchige, 2023; Shaffi et al., 2024).

Our study could not report on cancer outcomes due to the limited number of patients who underwent surgery and the challenges with consistent follow up. In a similar limited-resource setting, Shaffi et al. reported over 40 % lost to follow up in their 10-year review of cervical cancer management at the Moi Teaching and Referral Hospital in Kenya (Shaffi et al., 2024). UCI and Mulago Hospital are located adjacent to each other in Kampala, the largest city in Uganda. Many patients are referred from rural areas of the country making transportation to and from Kampala for clinic visits very challenging due to costs, time, and accessibility. Novel strategies such as coordinating oncology care at rural district health centers and regional hospitals may mitigate these follow up barriers. For example, in Uganda the level IV community health center in Kigandalo has been revamped to provide cancer services with referral to the closer regional hospital in Jinja where gynecologic oncology care is available. Furthermore, community integration of cancer care and prevention with involvement of community health workers play a crucial role in patient referral, follow up, and retention. Increasing the numbers of trained providers through local oncology fellowship programs can also improve access to care. Graduates from the UCI fellowships in gynecologic, pediatric and medical oncology currently practice at the Mbarara referral hospital in western Uganda. UCI is expanding oncology services to other regional hospitals in northern and northwest Uganda with plans to post graduating fellows at these sites.

Previous studies comparing NAC followed by radical hysterectomy compared to radical hysterectomy (RH) show clinical response rates to NAC of 52–84 % (Katsumata et al., 2013; Eddy et al., 2007; Sardi et al., 1997). Other trials have compared NAC followed by RH to radiation. In a phase III trial of NAC followed by RH compared to pelvic RT and brachytherapy for bulky Stage IB2-IIA, the overall clinical response to NAC was 86 % and there was no difference in disease free survival and overall survival between the two arms (Chang et al., 2000). Benedetti-Panici et al. included Stage IB2-III in their phase III study of 441 patients who underwent NAC and radical hysterectomy compared to radiation. In the NAC arm, 78 % were able to undergo RH and 26 % received additional chemotherapy or radiation after surgery if positive margins or nodes (Benedetti-Panici et al., 2002). The 5 year overall survival was improved in the NAC arm (59 % NAC vs 49 % RT, $p = 0.005$), with even greater differences for Stage IB2-IIB (65 % NAC vs 46 %RT, $p = 0.005$). In our resource-limited setting, only 15 % (8/53) of patients were able to complete planned surgery. Reasons for this may include limited blood availability and theatre space, the ongoing acquisition of clinical and surgical expertise by our institutions' oncology team during the study period, and logistics of scheduling surgery with an international mentor. At the UCI, theatre space included 2 operating tables and was shared with other surgical specialties. In addition, anesthesia coverage was a challenge due to limited workforce numbers. Blood availability was often in shortage and cases could not proceed if one unit of blood was not available prior to starting the case. Further study is needed to analyze how these logistical challenges may directly impact clinical decision making in resource-limited settings. Furthermore, limited access to whole body imaging to exclude patients who otherwise would not be candidates for NAC may have resulted in more advanced staged patients in our cohort. Patabendige et al. evaluated surgical assessment for cervical cancer without preoperative

imaging in their limited-resource setting and showed a 22 % upstage on final pathology due to lymph node metastasis (Patabendige et al., 2021).

More recently, results from two randomized trials examined NAC followed by surgery compared to current standard of care with chemoradiation in Stage IB2-IIB (Kenter et al., 2023; Gupta et al., 2018). The single center study of 633 patients by Gupta et al. showed worse 5 year disease free survival in the NAC surgery arm compared to chemoradiation (69.3 % vs 76.7 %, HR 1.38, 95 % CI 1.02–1.87). In the multicenter EORTC trial of 626 patients, there was no difference in the 5 year overall survival between NAC followed by surgery (72 %, 95 % CI 0.66–0.77) and chemoradiation (76 %, 95 % CI 0.70–0.80) (Kenter et al., 2023). In both studies, a significant number of the participants in the NAC surgery arm had adjuvant radiotherapy (44 % in Gupta et al. and 48 % in EORTC) and toxicities were acceptable in both arms. Although NAC followed by surgery has failed to demonstrate superiority over chemoradiation in Stage IB2-IIB, this may still be a viable strategy in resource-limited settings where radiation is not available.

Other limitations in our study include potential selection bias and incomplete documentation in the medical records. The number of deaths during this study period is likely higher and could not be accurately assessed given challenges with follow up. Our experience in conducting this study highlighted the challenges surrounding pathology including payment of tissue processing, limited number of pathologists, and need for more standardized surgical pathology reporting. In our study, two surgical patients were given additional adjuvant therapy due to incomplete pathology reports. Engaging pathologists in our monthly local Tumor Boards and developing standardized pathology forms has been helpful in improving surgical pathology reporting. The UCI has placed emphasis on pathology training. At the time of this study there was one UCI pathologist and currently, UCI has four pathologists.

In addition to transportation/geographic barriers, direct cost of care may have contributed to lost to follow up. Although the costs for cancer therapies (chemotherapy, surgery and radiation) are covered by the government, our study highlights potential discrepancies of health care coverage and what is expected from patients as costs were documented as reasons for discontinuation of therapy. Resources to understand and address proactively financial barriers are necessary and should be considered in future studies. Supportive medications such as pain medications are covered; however, challenges exist when drugs run out of stock. The effects of these factors to patient care could not be accurately extracted from available records in this study. Future investigation is needed to understand patient and health system barriers in obtaining cancer care in our setting in order to develop effective strategies to overcome noncompliance to recommended treatment.

The strength of our study includes our multidisciplinary collaboration to swiftly prioritize developing an alternative treatment strategy for cervical cancer patients in Uganda during 2016–2017. Early engagement of key stakeholders including providers in medical oncology, radiation oncology, and pathology was critical to take inventory of what was feasible and immediately available to patients. Established collaboration of experienced local gynecologic providers with international gynecologic oncologists provided additional support for developing treatment guidelines within standard of care practice. Despite the challenges faced by providers and patients, the majority of patients were able to receive and tolerate the recommended therapies. Our study highlights the feasibility of implementing the NCCN resource stratification framework to treatment guidelines based on available resources. More importantly, we have demonstrated the ability for the cancer care delivery team to pivot and adapt quickly to these challenges to avoid a lapse in cervical cancer treatment in Uganda.

CRediT authorship contribution statement

Jane Namugga: Writing – review & editing, Resources, Investigation, Data curation, Project administration. **Janice Wong:** Writing – review & editing, Formal analysis, Data curation. **Carolyn Nakisige:** Writing – review & editing, Supervision, Project administration, Investigation, Conceptualization. **Anthony Okoth:** Supervision, Resources, Conceptualization. **Judith Ajeani:** Supervision, Resources, Conceptualization. **Josephine Irene Najjemba:** Project administration, Data curation. **Stefanie Ueda:** Writing – review & editing, Supervision, Resources. **Paula S. Lee:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

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Conflict of interest statement

This study was supported by the Charles B. Hammond Research Fund. There were no conflicts of interest reported by all authors.

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