



Neoadjuvant chemotherapy and less invasive surgery for the management of early stage cervical cancer: A brief report from Botswana

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ABSTRACT

The majority of deaths from cervical cancer occur in low- and middle- income countries (LMICs). The standard of care for early-stage cervical cancer (FIGO 2018 IA2-IB1) is radical hysterectomy, a procedure performed by trained gynecologic oncologists. However, the lack of gynecologic oncologists in LMICs has required exploration into other methods of treatment for early-stage cervical cancer. A potential course of treatment for early-stage cervical cancer is neoadjuvant chemotherapy followed by simple hysterectomy and pelvic lymph node sampling, which can be performed by a general gynecologist. We gathered data for 8 women who underwent this method of treatment and found that cause-specific survival was 100% over a 3.5-year median follow-up. These findings support the exploration for this method of treatment for early-stage cervical cancer in LMICs, which would improve access to treatment for these women and hopefully reduce the high burden of cervical cancer related deaths in LMICs.

1. Introduction

Worldwide, there are more than 600,000 new cases and over 300,000 deaths from cervical cancer per year, with the majority occurring in low-and-middle-income countries (LMICs) (International Agency for Research on Cancer, 2020). Cervical cancer is the leading cause of cancer death in women in sub-Saharan Africa where the disease burden is further impacted by high HIV prevalence (Stelzle et al., 2021). While the standard of care treatment of early-stage disease (FIGO 2018 stage IA2 - IB1) is radical hysterectomy, there are a dearth of specialty trained gynecologic oncologists able to perform this surgery, especially in LMICs where the majority of cervical cancers occur (Lockett et al., 2018; Bradley et al., 2021). It has been shown that patients with cervical cancer treated by gynecologic oncologists have improved outcomes

(Sullivan et al., 2019).

In Botswana, approximately 25% of women with cervical cancer present with early stage disease that could be cured with radical surgery alone; however, until recently there were no trained gynecologic oncologists to perform these surgeries. (Lockett et al., 2018) Between 2017 and 2019, the lack of a specialty trained gynecologic oncologist in the country created an opportunity to evaluate other treatment modalities for early stage cervical cancer. The rationale for the use of neoadjuvant chemotherapy (NAC) in early-stage disease include reduction in tumor volume amenable to simple hysterectomy, and control of micro-metastatic disease (Miriayala et al., 2022; Rydzewska et al., 2012). While NAC followed by radical surgery has been unsuccessfully explored for patients with locally advanced cancers (Gupta et al., 2018), the role for NAC and less invasive surgery hasn't been well explored for

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management of early-stage cervical cancer (Kim et al., 2013).

2. Case presentations

In the absence of a gynecologic oncologist who would be able to perform a radical hysterectomy, we relied on the expertise of a clinical oncologist and general gynecologist to treat early-stage cervical cancer patients with NAC and simple hysterectomy and nodal sampling. This study was approved by the University of Pennsylvania Institutional Review Board, Princess Marina Hospital Institutional Review Board and the Ministry of Health and Wellness, Republic of Botswana under Expedited Review. Between 2017 and 2019, eight women were diagnosed with early-stage disease (stage IA2-IB1) and treated with NAC followed by a simple hysterectomy and pelvic lymph node sampling performed by a general gynecologist. Here we review their clinical, pathologic, and treatment outcomes. In all women, tumor size was <2 cm and there was an absence of lymphovascular space invasion during clinical exam and pre-op biopsy. Clinical staging included clinical pelvic exam, abdominal ultrasound, and chest x-ray prior to surgery. After confirmation of diagnosis with pre-op biopsy, patients were treated with three cycles of paclitaxel (paclitaxel (175 mg/m²) and carboplatin (dosed to an area under curve of 5–6) once every 3 weeks as per prior studies (Gupta et al., 2018; Kim et al., 2013; Cho et al., 2009). Patients then underwent simple hysterectomy with lymph node sampling at the discretion of general gynecologist.

Median follow-up for this cohort of women was 3.5 years. Patients were followed up every three months. Median age at surgery was 50 years (range 42–63). Six women (75%) had stage IB1 disease. Six women (75%) were HIV-positive, median CD4 count was 373.5 cells/uL. All patients had viral loads that were undetectable. Median of 8 nodes were sampled (see Table 1). Three patients (38%) had a pathologic complete response with no detectable tumor and 5 patients (62%) had a partial response with residual disease but negative margins on final surgical pathology. All patients were pathologically node negative. All patients completed chemotherapy as prescribed. None of the women had high-risk features warranting adjuvant therapy. One patient died 6 months after treatment due to a non-cancer related cause (accident). Overall survival for all patients was 87.5% (CI, 67.3%–100%) and cause-specific survival was 100% over a 3.5 year time-period.

3. Discussion and conclusions

These pilot data suggest favorable outcomes with NAC followed by a simple hysterectomy and pelvic nodal sampling for women with early-stage cervical cancer in Botswana. NAC followed by simple hysterectomy and pelvic lymph node sampling should be explored for early-stage cervical cancer, especially in settings with limited access to gynecologic oncologists. Historically, NAC has been utilized in two primary settings. The first with bulky cervical cancer followed by a radical hysterectomy to achieve radical operability and the second for fertility preserving surgery.

For bulky cervical tumors, neoadjuvant chemotherapy can improve pathologic prognostic factors for stage IB2-IIA bulky cervical cancer and to help avoid further adjuvant therapy. Cho et al. tested the efficacy of paclitaxel plus platinum NAC in patients with stage IB2 to IIA cervical cancer >4 cm, and determined that in the NAC group, a significantly lower proportion of patients were treated with NAC received post-operative radiation (42.9% vs 82.9%) than those undergoing primary surgery. Though, overall survival in the two groups were not statistically significant (Cho et al., 2009).

There has been a trend towards more conservative treatment in patients with early stage, low-risk cervical cancer, especially in the setting of fertility preservation (Rob et al., 2008). In a recent systematic review of articles that included neoadjuvant chemotherapy for fertility preservation, Gwacham et al. identified 18 manuscripts including 249 patients where 114 met the inclusion criteria of tumor size 2–4 cm and stage IB1

Table 1

Clinical and Outcomes Data of 8 women who received NAC and Simple Hysterectomy with Lymph Node Sampling.

	Age	# of lymph nodes sampled	Histology *Biopsy Specimen histology specified if surgical specimen does not demonstrate invasive cancer	LVSI	Stage	Outcomes
1	42	6	Invasive adenosquamous carcinoma of the cervix	negative	IB1	Alive at 4.5 years, no recurrence
2	53	4	Koilocytic CIN3	negative	IB1	Alive at 4 years, no recurrence
3	58	8	*Squamous cell carcinoma, moderately differentiated Koilocytotic CIN3	negative	IA2	Died, non-cancer related death at 2 years, no recurrence
4	48	10	*invasive squamous cell carcinoma, poorly differentiated	negative	IB1	Alive at 4 years, no recurrence
5	43	4	Infiltrating squamous cell carcinoma grade II	negative	IB1	Alive at 4 years, no recurrence
6	47	8	Invasive well differentiated nonkeratinizing squamous cell carcinoma	negative	IB2	Alive at 3.5 years, no recurrence
7	63	17	Moderately differentiated focally keratinizing squamous cell carcinoma	negative	IB1	Alive at 4 years, no recurrence
8	52	19	Squamous cell carcinoma grade II	negative	IB1	Alive at 3.5 years, no recurrence
			Invasive poorly differentiated squamous cell carcinoma	negative	IB1	Alive at 3.5 years, no recurrence

or IB2 cervical cancer. The most common NAC regimen was using cisplatin and paclitaxel with the addition of ifosfamide (89.5% of patients). Recurrence rate among this population was 6.1%, and 2/114 women died from the disease (Gwacham et al., 2021). This approach is being studied in an ongoing prospective trial, the CONTESSA trial, where the authors plan to test if neoadjuvant chemotherapy will be effective in reducing size of IB2 tumors to enable fertility sparing surgery in women, with outcomes including rate of functional uterus without adjuvant therapy (Plante et al., 2019).

The prior studies looked at bulkier tumors (IB2 to IIA) with a benefit of NAC and fertility sparing surgery. In our study population of early-stage tumors, data from ConCerv trial supports the lower risk of recurrence with conservative surgery. The ConCerv trial was a prospective single arm study where 100 women with Stage IA2-IB1 cervical cancer underwent conservative surgery with simple hysterectomy or cervical conization (based on desire for fertility preservation) as well as lymph node assessment. The 2-year recurrence rate was less than 4%. The results of this study further support the feasibility and safety of an intervention able to be performed by gynecologists without specific oncologic training, allowing for improved surgical care for women with cervical cancer in LMICs (Schmeler et al., 2021).

Availability of data and materials

Data sharing is not applicable to this article as no datasets were

generated or analyzed during the current study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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