RADICAL SURGERY FOR EARLY CERVICAL CANCER IN A RESOURCE-LIMITED SETTING: SURVIVAL AND CHALLENGES

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ABSTRACT

Introduction: Cervical cancer is one of the most common cancers affecting women, with the highest incidence and mortality rates reported in East Africa. This study aimed to evaluate the outcomes of patients with early-stage cervical cancer treated with radical surgery in Western Kenya.

Methodology: This was a retrospective study of 131 consecutive patients with early cervical cancer (FIGO stage IA2 - IIA) treated over 5 years at Moi Teaching and Referral Hospital in Western Kenya. Non-parametric statistics, the log-rank test and Cox regression were used to evaluate the effects of the covariates analysed on survival.

Results: The mean age was 44.8 years, and the modal age group was 41-50 years (38.9%). HIV seroprevalence was 45.8%, while squamous cell carcinoma was the predominant histologic type seen in 123 (93.9%) patients. The surgical margins were positive in 4 (3.1%) patients. Pelvic nodal metastases were seen in 42 (35.9%) patients. The number of patients who required adjuvant chemo-radiation was 51 (38.9%), but only 16 (31.4%) received it. All-cause mortality was 18.3%, with a five-year overall survival of 67.7%. The factors associated with mortality were age (HR=2.28, p <0.001), HIV positivity (HR=3.51, p=0.009), tumour size (HR=1.3, p=0.047), and use of neoadjuvant chemotherapy (HR= 2.70, p 0.033).

Conclusions: HIV seropositivity and age (per 10-year increase) are significant predictors of poor survival. The mechanism by which HIV negatively impacts survival requires further investigation.

Keywords: Survival, Early cervical cancer, Low resource

INTRODUCTION

Cervical cancer is one of the most common cancers affecting women. The 2018 GLOBOCAN report estimated that 569,847 women were diagnosed with cervical cancer worldwide, and most were in low and middle-income countries. Globally, the highest incidence and mortality is in East Africa (1). Following cervical cancer screening, women diagnosed with early-stage disease (IA2-IIA) have high cure rates with either radical hysterectomy (RH) or primary radiotherapy. Both modalities are associated with similar outcomes, with a five-year overall survival rate of 87%–92% (2). The choice of therapeutic modality is based on its availability and accessibility, patient co-morbidities, and patient or physician preference. Surgical treatment benefits include simultaneous lymphadenectomy for surgical staging (3) with possible therapeutic benefit (4),

preservation of ovarian function in premenopausal women, and improved coital function, as compared to primary radiotherapy (5-7).

In Western Kenya, access to radiation therapy is severely limited due to multiple factors, including few radiotherapy machines; hence, long wait times, high cost, and long travel distance to treatment facilities. Kenya has one public radiotherapy facility located in the nation's capital Nairobi, a distance of 300 kilometres from our centre in Eldoret. The other cheaper option for radiotherapy is in Uganda, the country neighbouring Kenya's western border, which offers both external beam and intra-cavitary treatment at about USD 1,000 less than in Kenya, but still an expenditure which most Kenyan women are unable to meet.

In Sub-Saharan Africa, efforts are being made to increase cervical cancer screening. In our setting at Eldoret, Western Kenya, a regional cervical cancer screening program was introduced in 2009 using Visual Inspection with Acetic Acid (VIA). As the screening became more available and accessible, early cervical cancers were diagnosed, and to cater for these women; we also established a parallel cancer treatment program to support the screening (8). A unique aspect of this program is its linkage to a long-standing established HIV/AIDS treatment program, the Academic Model Providing Access To Healthcare (AMPATH), which provides access to care for HIV-infected patients. Treatment algorithms were established in 2009 to manage stage I and II cervical cancers. These included primary surgery for small tumours and a combination of Neoadjuvant Chemotherapy (NACT) and surgery for bulky stage I and stage II tumours. Following protocol development and physician training through the gynaecologic oncology fellowship program, a cervical cancer treatment program was initiated at Moi Teaching and Referral Hospital in Eldoret, Kenya. From this program's inception to date, clinical data have been prospectively collected at the point of care for each patient undergoing surgery and neoadjuvant chemotherapy.

This study aims to demonstrate that with planning, organisation, and careful patient selection, surgery for early cervical can offer effective treatment in low resource settings. The study reports the surgical and pathological outcomes of patients with early-stage cervical carcinoma treated with radical surgery at Moi Teaching and Referral Hospital (MTRH), and can serve as an information source for other regions with high cervical cancer rates and limited resources. Additionally, it opens an opportunity for medical practitioners in high resource countries to assess our care process.

METHODOLOGY

All patient data were retrospectively collected from prospectively inputted data in a database maintained at the point of care. Where necessary, clinical charts, operative, and pathology reports were reviewed to ascertain completion of data. Additionally, and as part of our standard of care, patients and relatives were contacted by telephone to obtain further data. Ethical clearance was obtained from the institutional review board.

Radical surgery in our institution is by laparotomy and consist of an intermediate type II and type III radical hysterectomy with bilateral pelvic lymphadenectomy. Patients with large stage 1 or stage 2 tumours (largest diameter >4cm), who were not eligible for surgery at diagnosis, were treated with neoadjuvant chemotherapy (NACT). After every cycle, treatment response was assessed, and tumours that decreased in size, to 4cm or less, were then considered eligible for surgery. Patients' eligibility for either primary surgery or NACT/Surgery was agreed upon by clinicians at our multidisciplinary tumour board. Post-operatively and upon the review of final pathology, patients who were determined to be at higher risk of recurrence were recommended and referred for adjuvant chemoradiotherapy.

Disease-free Survival (DFS) was defined as the period between the date of surgery and the date of diagnosis of a recurrence or date of the last follow-up. In contrast, Overall Survival (O.S.) was defined as the period between surgery and date of death from any cause or date of the last follow-up. Postoperative mortality was defined as any death, regardless of cause, occurring within thirty days of surgery in or out of the hospital.

Data were analysed using R version 3.1.3 (9). Categorical variables were summarised as frequencies. Non-parametric statistics were used.

Continuous variables were summarised as medians, and their corresponding interquartile range (IQR). Gaussian assumptions were assessed empirically using the Shapiro Wilk test. The association between survival and covariates was evaluated using the log-rank test. Kaplan-Meier survival curves were used to describe the survival of the participants after surgery. Cox regression modelling was used to assess the factors that were jointly associated with mortality. The hazard ratios (H.R.), as well as the corresponding 95% confidence limits (95% CL), were reported.

RESULTS

From April 2010 to March 2015, 700 patients were diagnosed with cervical cancer, 561 patients (80.1%) having an advanced disease. The remaining 139 (19.9%) had early disease, and were consequently planned for radical surgery. The mean age of the patients was 44.8 years (range 22-79). Sixty-four (48.9%) patients had their tumors detected during routine cervical cancer screening (either by VIA or pap smear), and 2.3% were incidental findings. One hundred and twenty-three patients (93.9%) had squamous cell carcinoma while the remaining 8 (6.1%) had adenocarcinomas. No other histological types were represented. More than half (48.9%) of the patients were diagnosed after presenting to the hospital with symptoms, predominantly bleeding, malodorous vaginal discharge and pelvic pain. One hundred and thirty-one (131) patients (82 primary surgery and 49 NACT/Surgery) had their planned surgery completed, and their data was available for analysis. Intraoperatively, 8 patients (5.8%) had their surgery abandoned following examination under anaesthesia (EUA), where it was determined that their tumors were of higher stage and not amenable to surgical treatment. Sixty (45.8%) patients were HIV seropositive.

Five patients (4.9%) had positive surgical margins, while 47 (35.9%) had positive pelvic nodes (26 of those who had NACT/Surgery and 21 of those who had primary surgery) (Table 1). The median duration of surgery was 2.5 hours, and the median blood loss was 600 mls (range 300 – 800 mls), with 31 patients (23.7%) receiving an intraoperative blood transfusion. One or both ovaries were preserved in 54.9% of premenopausal patients.

Table 1: Pathological outcomes

Characteristic	Sample Size (n[a])	% (n/N)
Histological type		
Squamous	123	93.9
Adenocarcinoma	8	6.1
Surgical Margins		
Negative	126	96.2
Positive parametria	4	3.1
Positive vaginal	1	0.8
LVSI[b]		
Yes	2	1.5
No	4	3.1
Not stated	125	95.3
Pelvic Lymph Nodes		
Positive	47	35.9
Negative	84	64.1

[a]Total sample size (N) is 131 patients
[b]LVSI – Lympho-Vascular Space Invasion

Nine patients (6.9%) sustained at least one intraoperative injury that included: great vessel laceration (1), ureteric injury (5), and cystotomy (1). Post-operatively, 21 patients (16.0%) developed short-term morbidities (Table 2).

The 5-year Disease-Free Survival (DFS) was 91.7%. Over the follow-up period, 7 (5.3%) patients developed disease recurrence, all of them occurring within 24 months after surgery. All the patients whom cervical cancer recurred died (Figure 1).

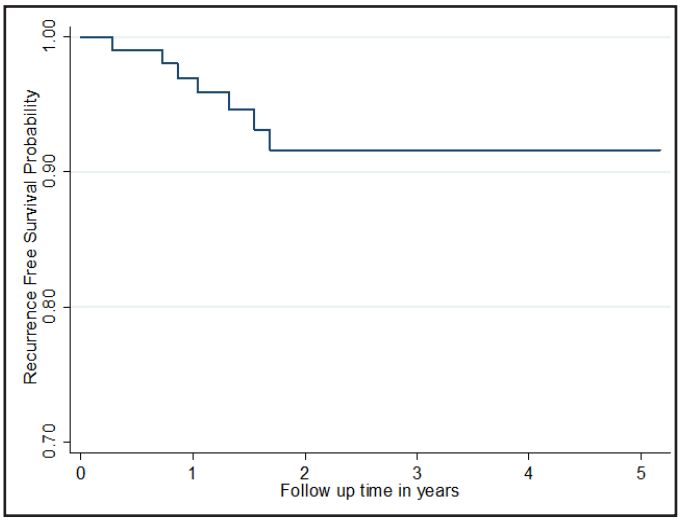

Figure 1: Disease-free survival curve

Table 2: Surgery and the outcomes

Characteristic	Sample size (N)	Description[c]	n (%)
Intraoperative Injuries	131	None	124 (94.6%)
		Great Vessel Laceration	1 (0.8%)
		Ureteric injury	5 (3.8%)
		Cystotomy	1 (0.8%)
		Pelvic Hemorrhage	2 (1.6%)
Short-time Morbidities	131	Febrile Morbidity	2 (1.5%)
		Paralytic Ileus	1 (0.8%)
		Wound Dehiscence	2 (1.5%)
		Fistula	1 (0.8%)
		DVT[d]	1 (0.8%)
		Infections (urinary, wound, pelvic)	8 (6.1%)
		Other	6 (4.6%)
Adjuvant Treatment Recommended	131	Yes	51 (38.9%)
		No	80 (61.1%)

[c]description of the types of outcomes intra- and post-operatively
[d]DVT - Deep Venous Thrombosis

A total of 24 deaths were reported during the follow-up period, giving a cumulative mortality rate of 18.3% (95% CL: 12.1, 26.0). Postoperative mortality was 2 (1.5%); one patient died of pulmonary thromboembolism, and the other died shortly after surgery due to anaesthetic-related complications.

The 5-year Overall Survival was 67.7%. Age, HIV positivity, tumour size, and need for neoadjuvant chemotherapy before surgery significantly negatively impacted survival (Table 3).

Table 3: Factors associated with mortality

Characteristic	HR (95% CI)	P-value
Age (per 10-year increase)	2.28 (1.45, 3.59)	<0.001
HIV positivity	3.52 (1.38, 9.01)	0.009
Tumour size (per centimeter increase)	1.30 (1.00, 1.67)	0.047
NACT/Surgery vs. Primary Surgery	2.70 (1.08, 6.72)	0.033

HR - Hazard Ratio
CI - Confidence Interval
NACT - Neoadjuvant Chemotherapy

The 5-year survival was 78.7% for HIV seronegative patients and 59.9% for HIV seropositive patients. The crude estimates show that the patients who received neoadjuvant chemotherapy before surgery had a higher mortality hazard than the patients who had primary surgery, crude H.R.: 3.86 (95% CI: 1.65, 9.08), P = 0.001 (Figure 2).

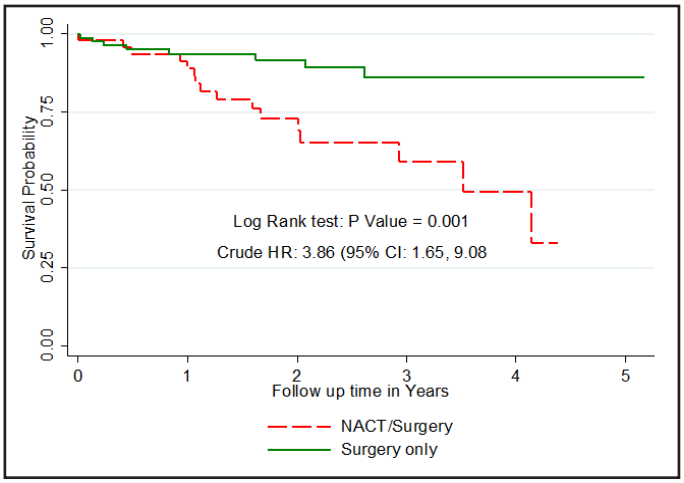

Figure 2: Survival distribution by treatment received

Upon adjusting for age, HIV status, and tumour size, the patients who received neoadjuvant chemotherapy (NACT) had significantly lower survival compared to those who had primary surgery (PS), (Adjusted HR 2.70 (95% CI: 1.08, 6.72, P=0.033) (Table 4).

The patients who underwent neoadjuvant chemotherapy were noted to have larger tumours, more pelvic nodal metastases, and a higher FIGO stage than those treated with primary surgery (Table 4).

Mortality was significantly higher in patients with pelvic nodal metastasis than those with negative nodes crude HR 2.55 (95% CI: 1.13, 5.74) (Figure 3).

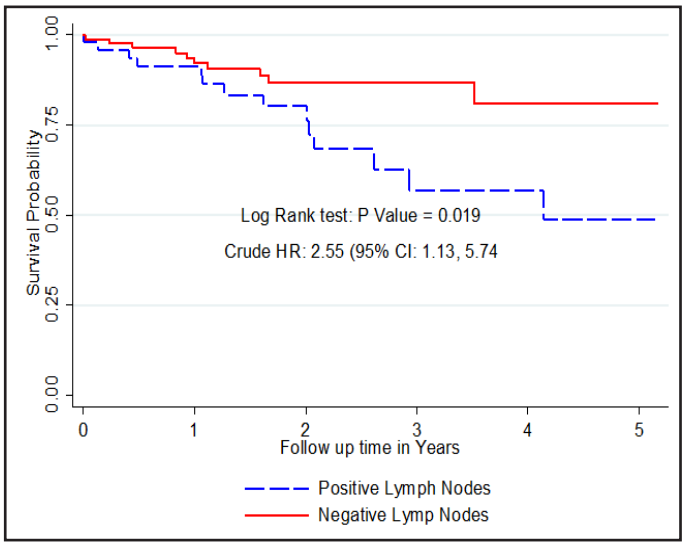

Figure 3: Survival distribution by the presence of lymph nodes metastases

Patients who required adjuvant treatment had significantly higher mortality p=0.019 (Figure 4). These are patients whose final pathology demonstrated at least one of the high-risk features for recurrence, such as positive margins (parametrial or vaginal), positive pelvic lymph nodes, or parametrial invasion.

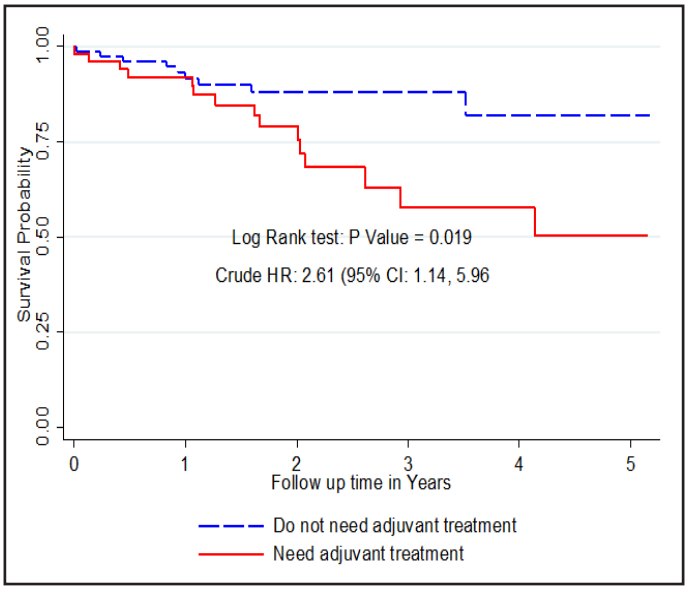

Figure 4: Survival distribution by a recommendation for adjuvant treatment

Table 4: Comparison of Primary Surgery and NACT/Surgery groups by various clinico-pathological characteristics.

Characteristic	NACT/Surgery n=49 (37.4%)	Primary Surgery n=82 (62.6%)	P value
	Mean(SD) or Median(IQR) or n(%)		
Age (years), Mean (SD)	45.0 (9.7)	44.8 (10.5)	0.918[t]
HIV Positive, n (%)	21 (42.9)	38 (46.3)	0.698[c]
Histology, n (%) **Adenocarcinoma** **SCC[e]**	 5 (10.2) 44 (89.8)	 3 (3.7) 79 (96.3)	 0.129[f]
Positive nodes, n (%)	26 (53.1)	21 (25.6)	0.002[c]
Tumour size (Mean diameter in mm), Median (IQR)	40 (20.0, 50.0)	20 (0.0, 30.0)	<0.0001[w]

Pearson's Chi-Square test; [f]Fisher's Exact test; [t] Independent samples t-test; [w] two sample Wilcoxon-rank sum test **IQR** – Interquartile Range; **SD**– Standard Deviation; [e]**SCC** – Squamous Cell Carcinoma

DISCUSSION

The 5-year Overall Survival rate was 67.7%, which compares unfavuorably with findings of other studies such as 80.7% in Turkey (10), 92.5% in the USA (11), and 87.2% in China (12). The relatively low survival in our population could be attributed to the massive HIV burden, a condition that was determined to impact negatively on survival. The 5-year Overall Survival for HIV infected patients in our population was significantly lower at 59.9% versus HIV negative patients of 78.7% despite them being otherwise similar in terms of age, tumour size, nodal metastases, and need for neoadjuvant chemotherapy before surgery. Over the entire follow-up period, 24 patients died from all causes giving an overall all-cause crude mortality rate of 18.3%. Two of these mortalities occurred during the early postoperative period resulting in operative mortality of 1.5%, comparable with the operative mortality of 1.4% reported in a 25-year prospective study but higher than 0.72% reported in a survey of 6992 radical hysterectomies done at various centres worldwide (13,14).

Patients who required adjuvant radiotherapy were referred to other centres due to non-availability of that service at our centre, and of the 51 patients for whom adjuvant radiation treatment was recommended, only 16 (31.4%) received the treatment. The failure to access the necessary adjuvant therapy negatively affected their survival. Age, tumour size, and the use of neoadjuvant chemotherapy were the other factors that negatively impacted survival. Nodal metastasis and FIGO stage also tended to impact negatively on survival. However, they did not reach statistical significance (likely due to the small sample size), unlike in other studies where both factors were significant (15).

Cervical cancer spreads through lymphatic channels to pelvic lymph nodes. The incidence of pelvic nodal metastasis in this study population was 35.9%, twice the rate reported by Averette et al. (13). Infrequent use of Computed Tomography (CT) scan imaging and operating on larger tumours after neoadjuvant chemotherapy in our series may explain this difference. Mortality was significantly higher among patients with pelvic nodal metastasis than those with negative pelvic nodes, which confirmed the findings of other studies that demonstrated nodal spread as a poor prognostic factor (16,17). HIV serostatus, however, did not predict nodal positivity. HIV seroprevalence among our study population was 45.8%, compared to a seroprevalence of 4.9% in Kenya's general population (18), which differed significantly from HIV seroprevalence in patients with the cervical carcinoma in Ibadan, Nigeria, and Tanzania reported as 2.7% (19) and 3.0% (20), respectively. One possible explanation for this variance is that our cervical cancer screening program, where most of our patients are drawn, is nested in the AMPATH HIV-care program. Subsequently, HIV infected women are over-represented.

The effect of lymphovascular space invasion could not accurately be assessed in this population since most pathological reports (95.3%) failed to mention or evaluate it. The study was carried out when the cervical cancer screening program was still in the infantile stage with minimal access to specialised pathology services.

Study strengths and limitations

Our study is the first structured and organised gynaecologic oncology to report data on outcomes from surgical treatment of cervical cancer in Sub-Saharan Africa. However, the nature of the study had an inherent limitation of being dependent on the integrity of the primary data that was documented.

CONCLUSIONS

Radical surgery for early cervical in low resource settings is associated with 67.7% survival. HIV seropositivity and older age are significant predictors of poor survival. The mechanism by which HIV disease negatively impacts cervical cancer patients' survival is unknown and requires further investigations.

Conflict of Interest: The authors declare no conflicts of interest.

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