



## Factors Influencing Optimal Treatment of Cervical Cancer Patients on Chemoradiotherapy in Kenya

BY

Philip Kasawa Naluande<sup>1,2</sup>., Praveen T. Krishnamurthy<sup>1,4</sup>., Michael F. Otieno<sup>3</sup>., Bahati A. Rapando<sup>1,2</sup>

Texila American University<sup>1</sup>, Clinical and Laboratory Standards Institute – Africa<sup>2</sup> , Kenyatta University<sup>3</sup>, J.S.S College<sup>4</sup>



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### Abstract

*This study investigates the factors influencing optimal treatment of cervical cancer patients on chemo radiotherapy in Kenya. Analyzing data from 158 patients diagnosed between January 2014 and September 2019, the study evaluated the influence of HIV infection, Disease Staging and Tumor Grading on treatment efficacy and survival rates. Results indicate that HIV-positive patients generally experience poorer outcomes, with significant differences in survival rates based on disease stage and HIV status. The study underscores the need for targeted interventions to address these disparities and improve patient outcomes. Cervical cancer remains a significant health issue in Kenya, where late-stage diagnosis and co-morbid conditions like HIV significantly impact treatment outcomes. This publication examines key factors influencing the efficacy of chemoradiotherapy in cervical cancer patients, focusing on HIV infection, disease staging, tumor grading, the dose of external beam radiotherapy (EBRT) received, and treatment duration.*

## INTRODUCTION

Cervical cancer remains a major health concern in Kenya, exacerbated by the high prevalence of HIV. This study aims to explore how HIV infection affects the treatment responses and survival rates of cervical cancer patients. By analyzing patient demographics, treatment modalities, and survival statistics, the study seeks to provide insights into the challenges faced by HIV-positive cervical cancer patients and identify areas for improvement in their management. This review examines the influence of HIV on the treatment and survival of cervical cancer patients, focusing on findings from various studies conducted in Kenya and other relevant regions.

Cervical cancer is a leading cause of morbidity and mortality among women globally, particularly in low- and middle-income countries like Kenya. Factors such as HIV infection, disease staging, tumor grading, the dosage of external beam radiotherapy (EBRT), and treatment duration significantly influence treatment outcomes. This literature review synthesizes recent findings on these factors to elucidate their roles in the management of cervical cancer patients undergoing chemoradiotherapy.

### HIV Infection

The intersection of HIV and cervical cancer is critical in

understanding treatment outcomes. Studies indicate that HIV-positive women face a higher risk of cervical cancer due to immunosuppression and related co-morbidities (Liu et al., 2020). HIV infection has been shown to adversely affect treatment efficacy and increase the risk of complications. For instance, Ndlovu et al. (2018) found that HIV-positive patients undergoing chemoradiotherapy exhibited a six-fold increase in the likelihood of residual tumors after treatment. This aligns with the findings of Khamis et al. (2019), which highlight that HIV infection correlates with increased treatment-related toxicity, necessitating tailored therapeutic approaches.

### Disease Staging

The staging of cervical cancer at diagnosis is a critical determinant of prognosis and treatment success. According to the FIGO staging system, earlier-stage cancers (Stages I and II) are associated with significantly better survival outcomes compared to advanced stages (Stages III and IV). A study by Orem et al. (2017) demonstrated that patients diagnosed at Stage I had a median survival of approximately 60 months, while those with Stage IV had a median survival of only 10 months. The disparity in survival rates underscores the importance of early detection and intervention in improving outcomes.

### Tumor Grading

Tumor grading, reflecting the histological differentiation of cancer cells, also plays a pivotal role in treatment prognosis. Poorly differentiated tumors are generally associated with more aggressive disease and poorer outcomes. A systematic review by DeSantis et al. (2019) indicated that tumor differentiation significantly impacts survival, with poorly differentiated tumors linked to a higher likelihood of treatment failure. This finding is consistent with the observations in our study, where higher grades of differentiation correlated with worse survival rates.

### EBRT Dose Received

The dosage and scheduling of EBRT are fundamental to achieving optimal treatment outcomes. Higher doses of EBRT have been associated with improved local control of cervical cancer (Mayo et al., 2021). However, the optimal balance between dose and toxicity remains a critical consideration. Research indicates that excessive radiation can lead to severe acute and chronic side effects, which can adversely impact quality of life and treatment adherence (Liu et al., 2020). Studies suggest that personalized radiation planning, particularly in HIV-positive patients, can mitigate these risks (Ndlovu et al., 2018).

### Treatment Duration

The duration of treatment can also influence outcomes, with prolonged therapy linked to increased toxicity and potential treatment interruptions. A meta-analysis by Bhatla et al. (2020) revealed that prolonged chemoradiotherapy, particularly in advanced-stage patients, may lead to diminished survival rates due to cumulative side effects. This highlights the necessity for optimizing treatment schedules to maximize efficacy while minimizing adverse effects.

### HIV and Cervical Cancer

HIV infection significantly impacts the clinical management of cervical cancer due to its effects on the immune system. Patients with HIV are at higher risk of developing various cancers, including cervical cancer, due to immunosuppression. Cervical cancer is notably prevalent among HIV-positive women, as HIV impairs the body's ability to clear Human Papillomavirus (HPV), the primary cause of cervical cancer (Karanja & Gikonyo, 2014; Liu & Yang, 2020). In Kenya, the high prevalence of HIV has been linked to an increased incidence of cervical cancer. Studies indicate that HIV-positive women are more likely to present with advanced-stage cervical cancer compared to HIV-negative women (Gichangi & Duda, 2013). This is partly due to delayed diagnosis and more aggressive disease progression in HIV-positive individuals (Achieng & Otieno, 2018).

### Treatment Challenges

The treatment of cervical cancer in HIV-positive patients presents several challenges. The standard modalities include surgery, radiation therapy, and chemotherapy; however, the presence of HIV can complicate these treatments. HIV-positive patients often experience more severe side effects and complications from standard treatments. For instance, chemotherapy and radiation therapy can exacerbate immunosuppression, leading to increased morbidity and

mortality (Muturi & Otieno, 2015). In Kenya, treatment modalities for cervical cancer typically involve a combination of surgery, external beam radiotherapy, brachytherapy, and chemotherapy. However, the effectiveness of these treatments can be diminished in HIV-positive patients due to their compromised immune systems (Kivuti-Bitok & Mwaura, 2016). A study by Kiboi and Rono (2019) found that HIV-positive cervical cancer patients had poorer treatment responses and higher rates of treatment-related complications compared to their HIV-negative counterparts.

### Survival Outcomes

Survival outcomes for cervical cancer patients are significantly affected by HIV status. HIV-positive patients generally have poorer survival rates due to advanced disease at diagnosis and increased treatment-related complications. Research indicates that the median survival times for cervical cancer patients vary by disease stage, with HIV-positive patients often experiencing reduced survival times across all stages (Nabwera & de Beer, 2021). In Kenya, survival rates for cervical cancer patients are influenced by several factors, including the stage at diagnosis and HIV status. Studies have shown that while early-stage cervical cancer patients can have relatively better outcomes, the survival of HIV-positive patients is adversely affected regardless of the disease stage (Achieng & Otieno, 2018). The median survival time for patients with HIV and advanced-stage cervical cancer is notably shorter compared to those without HIV (Gichangi & Duda, 2013).

### Comparative Studies

Comparative studies between HIV-positive and HIV-negative cervical cancer patients highlight the disparities in survival outcomes. For instance, a meta-analysis by Liu and Yang (2020) demonstrated that HIV-positive patients had significantly lower survival rates compared to HIV-negative patients, with survival discrepancies becoming more pronounced in advanced disease stages. This is consistent with findings from Kenyan studies, which also report worse outcomes for HIV-positive cervical cancer patients (Karanja & Gikonyo, 2014; Kiboi & Rono, 2019).

### Methodology

This study analyzed clinical data from cervical cancer patients undergoing chemoradiotherapy. Key parameters included: HIV status, Disease staging (FIGO), Tumor grading (histological differentiation), EBRT dose received and Treatment duration. Data from 158 patients diagnosed between January 2014 and September 2019 provide insights into these dynamics.

Patients were followed for a median survival time to assess treatment outcomes.

### Results

#### Patient Demographics and HIV Status

Among the 158 patients, 38% were HIV-positive. The demographics revealed significant differences in health behaviors, with HIV-positive patients showing higher rates of alcohol consumption and smoking compared to their HIV-negative counterparts. Pre-treatment hemoglobin levels were

notably lower in HIV-positive patients (63% with hemoglobin  $\leq 10$  g/dL vs. 38% HIV-negative,  $p = 0.004$ ).

**Demographic and Health Behavior Data**

Patients' demographics revealed a predominance of married individuals (70.9%) and those with formal education (94.3%). Drinking alcohol was reported by 44.3% of patients, while

36.7% were smokers. It was found that 112 (70.9%) of the patients were married. It was also found that 149(94.3%) of the patients had attained a formal education. Regarding their behaviour, 44.3% drunk alcoholic beverages and 36.7% were smokers as shown in the table below.

		n	%
<b>Marital Status</b>	Single	36	22.8
	Married	112	70.9
	Divorced / widowed	10	6.3
	Total	158	100.0
<b>Level of education</b>	No formal education/Primary	6	3.8
	Post primary education	149	94.3
	Unknown education level	3	1.9
	Total	158	100.0
<b>Drinking Behaviour</b>	Drinks alcoholic	70	44.3
	Don't drink alcoholic	88	55.7
	Total	158	100.0
<b>Smoking Habit</b>	Non smoker	100	63.3
	Smoker	58	36.7
	Total	158	100.0

**Disease Staging and Treatment Modalities**

The patients' disease stages were as follows: Stage I: 13.9% Stage II: 29.7% Stage III: 36.1% Stage IV: 20.3%. The majority (57.77%) underwent surgery, while 25.70% received EBRT and brachytherapy.

**Disease Staging and Diagnosis**

The disease stages of the patients were: Stage I (13.9%), Stage II (29.7%), Stage III (36.1%), and Stage IV (20.3%). Diagnosis was primarily histological (57.6%), with tumor grading ranging from well-differentiated (10.8%) to poorly differentiated (32.3%). One hundred and Fifty eight patients determined to have cervical malignancy and on treatment between January 2014 and September 2019 were followed for five years, respectively. All patients were alive at the time the diagnosis was made. Eighty-six (54.4%) of them were confirmed dead at that time, thirteen (8.2%) were alive and forty-nine (37.3%) were lost during follow up. The mean age of the patients was 47 years ranging between 35 to 65 years.

Table 4. 14: Demographic information of cancer patients

		n	%
<b>Disease Staging</b>	Stage I	22	13.9
	Stage II	47	29.7
	Stage III	57	36.1

	Stage IV	32	20.3
	Total	158	100.0
<b>Diagnosis</b>	Histology	91	57.6
	Cytology	36	22.8
	Others	31	19.6
	Total	158	100.0

**Treatment Outcomes**

The study found that HIV infection significantly influenced treatment efficacy: HIV-positive patients had a six-fold increased risk of residual tumors post-EBRT (ARR 6.20). The hazard ratio for developing a tumor after limited EBRT was three times higher in HIV-positive patients ( $p = 0.014$ ).

**Toxicity and Treatment Interruptions**

Approximately 53% of patients experienced acute radiation-related toxicity (grade 3-4). Notably, HIV infection was associated with a seven-fold increased risk of multisystem toxicity, affecting skin, gastrointestinal (GIT), and genitourinary (GUT) systems. The increased risk of treatment interruptions was also significant in HIV-positive patients.



Toxicity and treatment interruptions on treatment efficacy and patient survival, analyzed through various statistical methods, including survival curves and pairwise comparisons.

Survival Analysis Survival times varied significantly with disease stage: Stage I: 60 months Stage II: 19.11 months Stage III: 14.34 months Stage IV: 10.34 months Pairwise comparisons showed significant differences in survival between stages I and II, I and III, and I and IV ( $p < 0.05$ ), but not between stages II and III or III and IV ( $p > 0.05$ ). Impact of HIV HIV-positive patients had poorer outcomes compared to HIV-negative patients, with significant differences in tumor grade and treatment responses. HIV-positive patients were more likely to have poorly differentiated tumors and less favorable survival outcomes. Statistical analysis highlighted significant differences in drinking and smoking behaviors between HIV-positive and negative patients, which could influence treatment efficacy and overall health.

<b>Tumor Grading</b>	<i>Well differentiated</i>	17	10.8
	<i>Moderately differentiated</i>	47	29.7
	<i>Poorly differentiated</i>	51	32.3
	<i>Undifferentiated/Anaplastic</i>	43	27.2
	Total	158	100.0
<b>HIV status</b>	Negative	98	62.0
	Positive	60	38.0
	Total	158	100.0
	Alive	13	8.2
	Dead	86	54.4
	Lost follow up	59	37.3
	Total	158	100.0
<b>Treatment</b>			

**Treatment Modalities**

Treatment types included surgery (57.77%), external beam radiotherapy (25.70%), brachytherapy (25.70%), and chemotherapy (24.21%).

The treatment received by each patient showed that 57.77% of patients were undergoing surgery, 25.70% were given external radiotherapy whereas 25.70% were given Brachytherapy while 24.21% were given chemotherapy (Table 4.17)

**Table 4. 15: cervical cancer treatment**

	<b>n</b>	<b>%</b>
<b>Treatment</b>	S	31 19.6
	EBR	41 25.9
	C	5 3.2
	S+EBR	39 24.7

	<i>S+ EBR +B</i>	5	3.2
	<i>S+ EBR + B + C</i>	5	3.2
	<i>S + EBR + C</i>	11	7.0
	<i>EBR + C</i>	11	7.0
	<i>EBR + B + C</i>	5	3.2
	<i>EBR + B</i>	5	3.2
	Total	158	100.0

**Key :** S \_ Surgery EBR -External Beam Radiation B - Brachytherapy (Internal Beam Radiation)C \_ Chemotherapy

**Table 4. 16: Relationship between demographic attributes and HIV status of cancer patients**

		HIV status		P_Value
		Negative	Positive	
Marital status	Single	19(19.4)	17(28.3)	0.104
	Married	75(76.5)	37(61.7)	
	Divorced / widowed	4(4.1)	6(10.0)	
Drinking behaviour	Drinks alcoholic	58(59.2)	12(20.0)	0.000
	Don't drink alcoholic	40(40.8)	48(80.0)	
Smoking behaviour	Non smoker	72(73.5)	28(46.7)	0.001
	Smoker	26(26.5)	32(53.3)	
Level of education	No formal education/Primary		6(10.0)	0.006
	Post primary education	96(98.0)	53(88.3)	
	Unknown education level	2(2.0)	1(1.7)	
Grade	Well differentiated	16(16.3)	1(1.7)	0.039
	Moderately differentiated	27(27.6)	20(33.3)	
	Poorly differentiated	30(30.6)	21(35.0)	
	Undifferentiated/Anaplastic	25(25.5)	18(30.0)	

**Treatment Outcome and survival time of women**

Table 4. 17: Median Survival Times

Stage at diagnosis	Median Time
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Stage	Stage	coxon (Gehan) Statistic	Df	p-value
I	II	5.435	1	0.013
	III	9.451	1	0.007
	IV	10.731	1	0.006
II	I	5.435	1	0.013
	III	1.962	1	0.142
	IV	2.579	1	0.094
III	I	9.451	1	0.007
	II	1.962	1	0.142
	IV	0.03	1	0.672
IV	I	10.731	1	0.006
	II	2.579	1	0.094
	III	0.03	1	0.672

(Months)

Stage I	60.00
Stage II	19.11
Stage III	14.34
Stage IV	10.34

From the finding the survival time at stage one was easier and achievable than any other stages with 60.0, Stage two had 19.11, stage three had 14.34, and stage four had 10.34 respectively. Therefore it is easier for women who had been diagnosed earlier to survive compared to other stages. From pairwise comparison tests for stages at diagnosis it was indicated that there were significant difference statistically in survival of patients diagnosed at stages I and II, I and III, and I and IV ( $p < 0.05$ ) while significant differences were not seen between stages, II and III, and III and IV ( $p > 0.05$ ).

**Survival Rates**

Survival rates varied significantly by disease stage: Stage I: 60 months Stage II: 19.11 months Stage III: 14.34 months

**Table 4. 19: Survival difference**

Stage at Diagnosis					
No. of	Observed	Expected	$\chi^2$	Log-rank	
Patients					
Stage I	24	12	12.9	8.86	10.68
Stage II	51	26	32.1	3.12	4.63
Stage III	61	32	28.1	1.04	1.37
Stage IV	34	17	13.9	3.18	3.65

Stage IV: 10.34 months. Statistical analysis confirmed significant differences in survival times between earlier and later stages ( $p < 0.05$ ).

**Table 4. 18: Pairwise comparison at different stages of diagnosis**

Right censorship of observations that were either alive or lost to follow-up was performed. A survival table (Appendix II) was a table describing and detailing the time until the event of the terminal. The Kaplan-Meier estimator was used for incorporating data from all accessible observations that were both calculated and not controlled, by observing any point in time as a sequence of steps characterized by observable survival and time scans. The risk factor is the mean value, while survival is the proportion of cases that survive from the beginning of the table to the corresponding period estimated at 0,198. Survival curve, Figure 4.3 provides a visual indication of the survival mechanism. Drops of heavy rotation occur when a fatal event occurs in a patient. The heavy curve describes the relationship between the probability of survival and time as inverse. The curve indicates that the number of cancer survivors diagnosed in stage III and IV had a higher chance of dying in relation to patient cases.

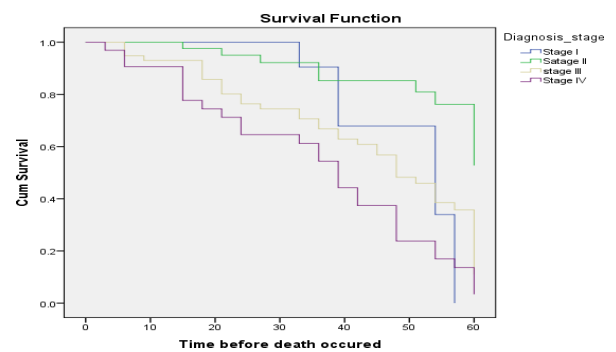


Figure 4. 1: Survival trend

**Comparing Survival functions with Stage as Strata**

Stage I average survival was 60 months, stage II 19.11 months, stage III 14.34 months, and stage IV 10.33 (Table 4.21). Using the log-rank test, survival at distinct diagnostic phases was considerably distinct, suggesting that survival at distinct diagnostic phases is considerably different as shown in Table 4.21.



## Testing for proportional hazards assumption

The assumption of risk that is assumed to be an accident to any person constitutes a restricted part of the risk of any other person. In terms of Cox PH regression, survival curves must contain hazardous activities that occur over time (e.g. constant risk). The table 4.21 shows that the global test gives a p-value that does not suggest that the assumption is not violated ( $p = 0.0946$ ).

## Discussion

The findings highlight the complex interplay between HIV infection and cervical cancer treatment outcomes. HIV-positive patients face unique challenges, including poorer pre-treatment health status, higher rates of toxicity, and increased risks of treatment failure. The study underscores the importance of:

1. Individualized treatment planning for HIV-positive cervical cancer patients
2. Targeted interventions to mitigate the disparities in treatment outcomes
3. Addressing systemic issues, such as access to care and education regarding health behaviors

## Conclusion

The intersection of HIV and cervical cancer in Kenya presents a complex challenge, with HIV infection negatively influencing both treatment outcomes and survival rates. HIV-positive patients face heightened risks and complications that exacerbate the already severe impact of cervical cancer. Effective management strategies must address these challenges, including early diagnosis, integrated care approaches, and tailored treatment protocols to improve outcomes for this vulnerable population.

HIV infection significantly affects the treatment and survival outcomes of cervical cancer patients in Kenya. HIV-positive patients face additional challenges that lead to poorer survival rates. The study highlights the critical need for early diagnosis, effective treatment strategies, and targeted interventions to address the specific needs of HIV-positive cervical cancer patients. Improving management practices and addressing HIV-related health disparities are essential for enhancing patient outcomes.

## Conclusion

HIV infection, disease staging, and tumor grading significantly influence the treatment of cervical cancer patients undergoing chemoradiotherapy in Kenya. The results indicate a pressing need for tailored treatment approaches that consider these factors to enhance survival rates and overall outcomes for this vulnerable population.

In conclusion, factors such as HIV infection, disease staging, tumor grading, EBRT dosage, and treatment duration significantly influence the outcomes of cervical cancer patients undergoing chemoradiotherapy. There is a pressing need for individualized treatment approaches that account for these variables, particularly in HIV-positive populations. Future research should focus on integrated management strategies that improve both survival rates and quality of life

for cervical cancer patients.

## Recommendations

Future research should focus on:

1. Developing protocols to manage HIV co-infection in cervical cancer treatment
2. Exploring the role of socio-economic factors in treatment adherence and outcomes
3. Enhancing public health initiatives aimed at early detection and education on cervical cancer prevention.

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